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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Jan 25  BLAST(R) searching in REGISTRY available in STN on the Web
 NEWS  3  Jan 29  FSTA has been reloaded and moves to weekly updates
 NEWS  4  Feb 01  DKILIT now produced by FIZ Karlsruhe and has a new update
                  frequency
 NEWS  5  Feb 19  Access via Tymnet and SprintNet Eliminated Effective 3/31/02
 NEWS  6  Mar 08  Gene Names now available in BIOSIS
 NEWS  7  Mar 22  TOXLIT no longer available
 NEWS  8  Mar 22  TRCTHERMO no longer available
 NEWS  9  Mar 28  US Provisional Priorities searched with P in CA/CAplus
                  and USPATFULL
 NEWS 10  Mar 28  LIPINSKI/CALC added for property searching in REGISTRY
 NEWS 11  Apr 02  PAPERCHEM no longer available on STN.  Use PAPERCHEM2 instead.
 NEWS 12  Apr 08  "Ask CAS" for self-help around the clock
 NEWS 13  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS 14  Apr 09  ZDB will be removed from STN
 NEWS 15  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS 16  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
 NEWS 17  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS 18  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS 19  Jun 03  New e-mail delivery for search results now available
 NEWS 20  Jun 10  MEDLINE Reload
 NEWS 21  Jun 10  PCTFULL has been reloaded
 NEWS 22  Jul 02  FOREGE no longer contains STANDARDS file segment

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
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FILE 'HOME' ENTERED AT 12:18:33 ON 09 JUL 2002

=>  file medline caplus embase biosis
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
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FILE 'BIOSIS' ENTERED AT 12:18:45 ON 09 JUL 2002
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=> s (nef (1N) (84-92)) or (GAG (1N) 77-85)
L1          20 (NEF (1N) (84-92)) OR (GAG (1N) 77-85)

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2           5 DUP REM L1 (15 DUPLICATES REMOVED)

=> dis l2 ibib abs 1-5

L2   ANSWER 1 OF 5     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   2002216247     IN-PROCESS
DOCUMENT NUMBER:    21948637   PubMed ID: 11952141
TITLE:              Differential processing of HLA A2-restricted HIV type 1
                    cytotoxic T lymphocyte epitopes.
AUTHOR:             Sewell Andrew K; Booth Bruce L Jr; Cerundolo Vincenzo;
                    Phillips Rodney E; Price David A
CORPORATE SOURCE:   Nuffield Department of Clinical Medicine, John Radcliffe
                    Hospital, Oxford, United Kingdom.. andy.sewell@ndm.ox.ac.uk
SOURCE:             VIRAL IMMUNOLOGY, (2002) 15 (1) 193-6.
                    Journal code: 8801552. ISSN: 0882-8245.
PUB. COUNTRY:       United States
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20020416
                    Last Updated on STN: 20020416
AB   Cytotoxic T lymphocytes (CTLs) play a key role in the control of
     persistent viral infections. Differences in the quality of this cellular
     immune response influence the long-term outcome of such infections, but
     the factors that determine which virus-derived peptide epitopes are
```

targeted by CTLs remain poorly understood. Here, we examine the antigen-processing requirements of three human leukocyte antigen (HLA) A*0201-restricted HIV-1 CTL epitopes. Each of these three peptides appears to be generated by a distinct proteolytic pathway, despite presentation on the cell surface in association with the same HLA class I molecule. Presentation of the commonly immunodominant SLYNTVATL (HIV-1 p17 Gag; residues 77-85) epitope was unaffected by inhibition of the proteasome with lactacystin, but was dependent on the presence of the beta-subunit LMP7. These findings are consistent with emerging data on the complexity of peptide epitope generation, and suggest that differences in antigen processing might contribute to patterns of CTL recognition in vivo.

L2 ANSWER 2 OF 5 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001256877 MEDLINE
DOCUMENT NUMBER: 21067100 PubMed ID: 11148222
TITLE: Substantial differences in specificity of HIV-specific cytotoxic T cells in acute and chronic HIV infection.
AUTHOR: Goulder P J; Altfeld M A; Rosenberg E S; Nguyen T; Tang Y; Eldridge R L; Addo M M; He S; Mukherjee J S; Phillips M N; Bunce M; Kalams S A; Sekaly R P; Walker B D; Brander C
CORPORATE SOURCE: Partners AIDS Research Center, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, USA.. goulder@helix.mgh.harvard.edu
CONTRACT NUMBER: AI01541 (NIAID)
AI28568 (NIAID)
AI46995 (NIAID)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (2001 Jan 15) 193 (2) 181-94.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB Cytotoxic T lymphocytes (CTLs) play a vital part in controlling viral replication during human viral infections. Most studies in human infections have focused on CTL specificities in chronic infection and few data exist regarding the specificity of the initial CTL response induced in acute infection. In this study, HIV-1 infection in persons expressing human histocompatibility leukocyte antigen (HLA)-A*0201 was used as a means of addressing this issue. In chronic infection, the dominant HLA-A*0201-restricted CTL response is directed towards the epitope SLYNTVATL (*SL9*) in p17 Gag (residues 77-85). This epitope is targeted by 75% of HLA-A*0201-positive adults, and the magnitude of this A*0201-SL9 response shows a strong negative association with viral load in progressive infection. Despite using the highly sensitive peptide-major histocompatibility complex tetramer and intracellular cytokine assays, responses to the SL9 epitope were not detectable in any of 11 HLA-A*0201-positive subjects with acute HIV-1 infection (P = 2 x 10(-6)), even when assays were repeated using the SL9 peptide variant that was encoded by their autologous virus. In contrast, multiple responses (median 3) to other epitopes were evident in 7 of the 11 A*0201-positive subjects. Longitudinal study of two subjects confirmed that the A*0201-SL9 response emerged later than other CTL responses, and after viral set point had been reached. Together, these data show that the CTL responses that are present and that even may dominate in chronic infection may differ substantially from those that constitute the initial antiviral CTL response. This finding is an important consideration in vaccine design and in the evaluation of vaccine candidates.

L2 ANSWER 3 OF 5 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001548908 MEDLINE
DOCUMENT NUMBER: 21479466 PubMed ID: 11595297
TITLE: Mother-to-child transmission of HIV infection and CTL escape through HLA-A2-SLYNTVATL epitope sequence variation.
AUTHOR: Goulder P J; Pasquier C; Holmes E C; Liang B; Tang Y; Izopet J; Saune K; Rosenberg E S; Burchett S K; McIntosh K; Barnardo M; Bunce M; Walker B D; Brander C; Phillips R E
CORPORATE SOURCE: Department of Paediatrics, Nuffield Department of Medicine, Level 7, Room 7615, John Radcliffe Hospital, Oxford OX3 9DU, UK.. philip.goulder@ndm.ox.ac.uk
CONTRACT NUMBER: AI 01541 (NIAID)
AI28568 (NIAID)
AI30914 (NIAID)
AI46995 (NIAID)
SOURCE: IMMUNOLOGY LETTERS, (2001 Nov 1) 79 (1-2) 109-16.
Journal code: 7910006. ISSN: 0165-2478.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20011015
Last Updated on STN: 20020209
Entered Medline: 20020208

AB Cytotoxic T lymphocytes (CTL) play a central role in containment of HIV infection. Evasion of the immune response by CTL escape is associated with progression to disease. It is therefore hypothesised that transmitted viruses encode escape mutations within epitopes that are required for successful control of viraemia. In order to test this hypothesis, escape through the dominant HLA-A2-restricted CTL epitope SLYNTVATL (p17 Gag residues 77-85 SL9) in the setting of mother-to-child-transmission (MTCT) was investigated. Initial data from two families in which the HIV-infected mother expressed HLA-A*0201 and had transmitted the virus to other family members were consistent with this hypothesis. In addition, analysis of the gag sequence phylogeny in one family demonstrated that CTL escape variants can be successfully transmitted both horizontally and vertically. To test the hypothesis further, a larger cohort of transmitting mothers (n=8) and non-transmitters (n=14) were studied. Variation within the SL9 epitope was associated with expression of HLA-A2 (P=0.04) but overall no clear link between variation from the SL9 consensus sequence and MTCT was established. However, the high level of background diversity within p17 Gag served to obscure any possible association between escape and MTCT. In conclusion, these studies highlighted the obstacles to demonstrating CTL escape arising at this particular epitope. Alternative strategies likely to be more definitive are discussed.

L2 ANSWER 4 OF 5 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 1998282291 MEDLINE
DOCUMENT NUMBER: 98282291 PubMed ID: 9616227
TITLE: Lack of strong immune selection pressure by the immunodominant, HLA-A*0201-restricted cytotoxic T lymphocyte response in chronic human immunodeficiency virus-1 infection.
AUTHOR: Brander C; Hartman K E; Trocha A K; Jones N G; Johnson R P; Korber B; Wentworth P; Buchbinder S P; Wolinsky S; Walker B D; Kalams S A
CORPORATE SOURCE: AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA.
CONTRACT NUMBER: R01 AI 33327 (NIAID)
R01 AI30914 (NIAID)
R37 AI28568 (NIAID)
+
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1998 Jun 1) 101 (11) 2559-66.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980713
Last Updated on STN: 19980713
Entered Medline: 19980626

AB Despite detailed analysis of the HIV-1-specific cytotoxic T lymphocyte response by various groups, its relation to viral load and viral sequence variation remains controversial. We analyzed HLA-A*0201 restricted cytotoxic T lymphocyte responses in 17 HIV-1-infected individuals with viral loads ranging from < 400 to 221,000 HIV RNA molecules per milliliter of plasma. In 13 out of 17 infected subjects, CTL responses against the SLYNTVATL epitope (p17 Gag; aa 77-85) were detectable, whereas two other HLA-A*0201 restricted epitopes (ILKEPVHGV, IV9; and VIYQYMDDL, VL9) were only recognized by six and five individuals out of 17 individuals tested, respectively. Naturally occurring variants of the SL9 epitope were tested for binding to HLA-A*0201 and for recognition by specific T cell clones generated from five individuals. Although these variants were widely recognized, they differed by up to 10,000-fold in terms of variant peptide concentrations required for lysis of target cells. A comparison of viral sequences derived from 10 HLA-A*0201-positive individuals to sequences obtained from 11 HLA-A*0201-negative individuals demonstrated only weak evidence for immune selective pressure and thus question the in vivo efficacy of immunodominant CTL responses present during chronic HIV-1 infection.

L2 ANSWER 5 OF 5 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 95016420 MEDLINE
DOCUMENT NUMBER: 95016420 PubMed ID: 7523570
TITLE: Naturally processed viral peptides recognized by cytotoxic T lymphocytes on cells chronically infected by human immunodeficiency virus type 1.
AUTHOR: Tsomides T J; Aldovini A; Johnson R P; Walker B D; Young R A; Eisen H N
CORPORATE SOURCE: Center for Cancer Research, Massachusetts Institute of Technology, Cambridge 02139.
CONTRACT NUMBER: AI-26463 (NIAID)
AI-34247 (NIAID)
R35 CA-42504 (NCI)
+
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Oct 1) 180 (4) 1283-93.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19960129
Entered Medline: 19941102

AB We have established long-term cultures of several cell lines stably and uniformly expressing human immunodeficiency virus type 1 (HIV-1) in order to (a) identify naturally processed HIV-1 peptides recognized by cytotoxic T lymphocytes (CTL) from HIV-1-seropositive individuals and (b) consider the hypothesis that naturally occurring epitope densities on HIV-infected cells may limit their lysis by CTL. Each of two A2-restricted CD8+ CTL specific for HIV-1 gag or reverse transcriptase (RT) recognized a single naturally processed HIV-1 peptide in trifluoroacetic acid (TFA) extracts of infected cells: gag 77-85 (SLYNTVATL) or RT 476-484 (ILKEPVHGV). Both processed peptides match the synthetic peptides that are optimally active in cytotoxicity assays and have the consensus motif described for A2-associated peptides. Their abundances were approximately 400 and approximately 12 molecules per infected Jurkat-A2 cell, respectively. Other synthetic HIV-1 peptides active at subnanomolar concentrations were not present in infected cells. Except for the antigen processing mutant line T2, HIV-infected HLA-A2+ cell lines were specifically lysed by both A2-restricted CTL, although infected Jurkat-A2 cells were lysed more poorly by RT-specific CTL than by gag-specific CTL, suggesting that low cell surface density of a natural peptide may limit the effectiveness of some HIV-specific CTL despite their vigorous activity against synthetic peptide-treated target cells.

=> s analogue
L3 207502 ANALOGUE

=> s l2 and l3
L4 0 L2 AND L3

=> dis his

(FILE 'HOME' ENTERED AT 12:18:33 ON 09 JUL 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:18:45 ON 09 JUL 2002
L1 20 S (NEF (1N) (84-92)) OR (GAG (1N) 77-85)
L2 5 DUP REM L1 (15 DUPLICATES REMOVED)
L3 207502 S ANALOGUE
L4 0 S L2 AND L3

=> s l1 and l3
L5 0 L1 AND L3

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=>

=> s l3 and HIV
L6         4675 L3 AND HIV

=> s l3 (P) (peptide? or protein?)
L7        46831 L3 (P) (PEPTIDE? OR PROTEIN?)

=> s l7 (P) AIDS
L8          184 L7 (P) AIDS

=> s l7 (P) (HIV or NEF or AIDS)
L9          801 L7 (P) (HIV OR NEF OR AIDS)

=> s l7 (P) (HIV or NEF or AIDS or GAG)
L10         847 L7 (P) (HIV OR NEF OR AIDS OR GAG)

=> s l7 (P) (NEF or GAG)
L11         110 L7 (P) (NEF OR GAG)

=> s l11 and PD<19980507
'19980507' NOT A VALID FIELD CODE
   3 FILES SEARCHED...
L12          64 L11 AND PD<19980507

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13          41 DUP REM L12 (23 DUPLICATES REMOVED)

=> dis l13 1-41 ibib abs

L13  ANSWER 1 OF 41  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:    1998:490879  BIOSIS
DOCUMENT NUMBER:     PREV199800490879
TITLE:               RNA structure inhibits the TRAP (trp RNA-binding
                     attenuation protein)-RNA interaction.
AUTHOR(S):           Xirasagar, Sandhya; Elliott, Matthew B.; Bartolini, Wilmin;
                     Gollnick, Paul; Gottlieb, Philip A. (1)
CORPORATE SOURCE:    (1) Dep. Biol. Sci., State Univ. N.Y. Buffalo, Buffalo, NY
                     14260 USA
SOURCE:              Journal of Biological Chemistry, (Oct. 16, 1998)
                     Vol. 273, No. 42, pp. 27146-27153.
                     ISSN: 0021-9258.
DOCUMENT TYPE:       Article
LANGUAGE:            English
AB   TRAP (trp RNA-binding Attenuation protein) regulates expression
     of the tryptophan biosynthetic genes in response to tryptophan in Bacillus
     subtilis by binding to two sites containing a series of 9 or 11 (G/U)AG
     triplet repeats that are generally separated by two or three spacer
     nucleotides. Previous mutagenesis experiments have identified three TRAP
     residues, Lys-37, Lys-56, and Arg-58 that are essential for RNA binding.
     The location of these residues on the TRAP oligomer supports the proposal
     that RNA binds TRAP by encircling the TRAP oligomer. In this work, we show
     that RNAs containing 11 GAG or UAG repeats separated by CC
     dinucleotide spacers (((G/U)AGCC)11) form stable structures that inhibit
     binding to TRAP. This conclusion is based on the effects of temperature
     and Mg2+ on the affinity of TRAP for RNAs with CC spacers combined with UV
     hyperchromicity and circular dichroism. Furthermore, introducing the base
     analogue 7-deazaguanosine in the ((G/U)AGCC)11 RNAs stabilized the
     TRAP-RNA interaction. This effect was associated with decreased stability
     of the RNA structure as measured by circular dichroism spectroscopy. The
     precise nature of the structure of the ((G/U)AGCC)11 RNAs is not known but
     evidence is presented that it involves noncanonical interactions. We also
     observed that substitution of Arg-58 with Lys further reduced the ability
     of TRAP to interact with structured RNAs. Since in vivo function of TRAP
     may involve binding to structured RNAs, we suggest a potential function
     for this residue, which is conserved in TRAP from three different bacilli.

L13  ANSWER 2 OF 41  EMBASE  COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER:    1998117456  EMBASE
TITLE:               Serological detection of attenuated HIV-1 variants with nef
                     gene deletions.
AUTHOR:              Greenway AL.; Mills J.; Rhodes D.; Deacon N.J.; McPhee D.A.
CORPORATE SOURCE:    D.A. McPhee, ACBU, National Ctr. HIV Virology Res.,
                     Macfarlane Burnet Ctr. Medical Res., PO Box 254, Fairfield,
                     Vic 3078, Australia
SOURCE:              AIDS, (16 Apr 1998) 12/6 (555-561).
                     Refs: 24
                     ISSN: 0269-9370  CODEN: AIDSET
COUNTRY:             United Kingdom
DOCUMENT TYPE:       Journal; Article
FILE SEGMENT:        004     Microbiology
                     026     Immunology, Serology and Transplantation
LANGUAGE:            English
SUMMARY LANGUAGE:    English
AB   Objective: To investigate whether members of a transfusion-linked cohort
     (the Sydney Bloodbank Cohort) infected with a nef-deleted strain
     of HIV-1 could be differentiated from individuals infected with wild-type
     strains of HIV-1 by characterizing the Nef antibody response of
     cohort members. Design: Retrospective and prospective analysis of the
     nef gene sequence and the antibody response to Nef
     peptides in HIV-infected subjects. Methods: Plasma was obtained
     from all individuals of the Sydney cohort, and from a variety of
     HIV-1-infected and uninfected controls. Antibodies recognizing full-length
     recombinant HIV-1(NL43) Nef protein and synthetic
     peptide analogues were assessed by enzyme-linked
     immunosorbent assay. Results: All 34 individuals infected with wild-type
     HIV-1 had antibodies reacting with lull-length Nef
     protein as well as with a series of synthetic peptides
     (6-23-mers) spanning most of the Nef protein of
     HIV-1(NL43). Although the HIV-1 quasispecies infecting the Sydney cohort
     had a consensus deletion of the nef gene corresponding to
     amino-acids 165-206, HIV-1 strains from individual members of the cohort
     had additional deletions comprising up to 80% of the nef gene.
     Members of the cohort had antibodies to peptides homologous to
     all regions of the Nef protein tested, except for a
     single peptide (amino-acids 162-177) that lies within the
     consensus nef deletion for the cohort quasispecies. Conclusion:
     These data show that nef-deleted strains of HIV-1 can be
     detected serologically. In the Sydney cohort, detection of antibodies to
     all regions of Nef tested, except that corresponding to
     amino-acids 162-177, suggests that observed deletions outside this domain
```

occurred after this virus had infected these subjects and stimulated an immune response. A Nef peptide serological assay may be useful for identifying further examples of individuals infected with nef-deleted, attenuated HIV-1 quasispecies and for assessing the evolution of those variants in vivo.

L13 ANSWER 3 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 1998092248 EMBASE
TITLE: Immune response to recombinant visna virus Gag and Env precursor proteins synthesized in insect cells.
AUTHOR: Rafnar B.; Tobin G.J.; Nagashima K.; Gonda M.A.; Gunnarsson E.; Andresson S.; Georgsson G.; Torsteinsdottir S.
CORPORATE SOURCE: B. Rafnar, Institute for Experimental Pathology, University of Iceland, Keldur, IS-112 Reykjavik, Iceland
SOURCE: Virus Research, (1998) 53/2 (107-120).
Refs: 54
ISSN: 0168-1702 CODEN: VIREDF
PUBLISHER IDENT.: S 0168-1702(97)00141-X
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Two different recombinant visna virus (VV) gag-baculoviruses were constructed for the expression of precursor VV Gag in insect cells. Both recombinant Gag viruses expressed proteins migrating on SDS-PAGE at the predicted rate for VV Gag precursor, Pr50(gag). However, differences were seen in the morphology of the virus-like particles produced. Monoclonal antibody directed against the VV Gag capsid protein (p25) and sera from sheep infected with ovine lentiviruses reacted to both 50-kDa proteins. A recombinant VV env-baculovirus was constructed, substituting sequences encoding the signal peptide of VV Env with the murine IFN-.gamma. analogue. Sera from ovine lentivirus infected sheep reacted in immunoblots with two proteins of approximately 100 and 200 kDa found in the plasma membrane of insect cells infected with env-recombinant virus. Sheep immunized with either the recombinant Gag or the Env proteins developed high antibody titers to VV in ELISA. The serum of sheep and ascitic fluid of mice immunized with the recombinant Gag reacted with native Pr50(gag) and the processed Gag proteins in immunoblots, whereas serum of the recombinant Env immunized sheep reacted with VV gp135 and a putative oligomer of gp135. The immunized sheep responded specifically to visna virus by lymphocyte proliferation in vitro. Copyright (C) 1998 Elsevier Science B.V.

L13 ANSWER 4 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 97309508 EMBASE
DOCUMENT NUMBER: 1997309508
TITLE: Transfer of the HIV-1 cyclophilin-binding site to simian immunodeficiency virus from Macaca mulatta can confer both cyclosporin sensitivity and cyclosporin dependence.
AUTHOR: Bukovsky A.A.; Weimann A.; Accola M.A.; Gottlinger H.G.
CORPORATE SOURCE: A.A. Bukovsky, Division of Human Retrovirology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1997) 94/20 (10943-10948).
Refs: 33
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB HIV-I specifically incorporates the peptidyl prolyl isomerase cyclophilin A (CyPA), the cytosolic receptor for the immunosuppressant cyclosporin A (CsA). HIV-1 replication is inhibited by CsA as well as by nonimmunosuppressive CsA analogues that bind to CyPA and interfere with its virion association. In contrast, the related simian immunodeficiency virus SIVmac, which does not interact with CYPA, is resistant to these compounds. The incorporation of CyPA into HIV-I virions is mediated by a specific interaction between the active site of the enzyme and the capsid (CA) domain of the HIV-1 Gag polyprotein. We report here that the transfer of HIV-1 CA residues 86-93, which form part of an exposed loop, to the corresponding position in SIVmac resulted in the efficient incorporation of C.apprx.PA and conferred an HIV-1-like sensitivity to a nonimmunosuppressive cyclosporin. HIV-1 CA residues 86-90 were also sufficient to transfer the ability to efficiently incorporate CyPA, provided that the length of the C.apprx.PA binding loop was preserved. However, the resulting SIVmac mutant required the presence of cyclosporin for efficient virus replication. The results indicate that the presence or absence of a type II tight turn adjacent to the primary CyPA-binding site determines whether CyPA incorporation enhances or inhibits viral replication. By demonstrating that CyPA-binding-site residues can induce cyclosporin sensitivity in a heterologous context, this study provides direct in vivo evidence that the exposed loop between helices IV and V of HIV-! CA not merely constitutes a docking site for CyPA but is a functional target of this cellular protein.

L13 ANSWER 5 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4
ACCESSION NUMBER: 97125376 EMBASE
DOCUMENT NUMBER: 1997125376
TITLE: The non-immunosuppressive cyclosporin A analogue SDZ NIM 811 inhibits cyclophilin A incorporation into virions and virus replication in human immunodeficiency virus type 1-infected primary and growth-arrested T cells.
AUTHOR: Mlynar E.; Bevec D.; Billich A.; Rosenwirth B.; Steinkasserer A.
CORPORATE SOURCE: A. Steinkasserer, Immuno-AG, Div. Oncog. Viruses, Benatzkygasse 2-6, A-1220 Vienna, Austria
SOURCE: Journal of General Virology, (1997) 78/4 (825-835).
Refs: 35
ISSN: 0022-1317 CODEN: JGVIAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
AB SDZ NIM 811 is a cyclosporin A (CsA) analogue that is completely devoid of immunosuppressive capacity but exhibits potent and selective antihuman immunodeficiency virus type 1 (HIV-1) activity. Binding to cyclophilin A, the intracellular receptor for cyclosporins, is a prerequisite for HIV-1 inhibition by cyclosporins. Cyclophilin A was demonstrated to bind to HIV-1 p24(gag) and this cyclophilin-Gag interaction leads to the incorporation of cyclophilin A into HIV-1 virions. SDZ NIM 811 inhibits this protein interaction, and this is likely to be the molecular basis for its antiviral activity. Here, we show that in activated primary T cells SDZ NIM 811 interferes with two stages of the virus replication cycle: (i) translocation of pre-integration complexes into the nucleus and (ii) production of infectious virus particles. SDZ NIM 811 not only inhibits translocation of HIV-1 pre-integration complexes in primary T cells, but also in a growth-arrested T cell line. In vivo, most T lymphocytes are quiescent, but serve nevertheless as a major and inducible HIV-1 reservoir in infected individuals. Significant amounts of cyclophilin A were found to be associated with virus particles propagated in primary T cells. SDZ NIM 811 caused a strong reduction in the amount of incorporated cyclophilin A, thereby reducing infectivity. Thus, cyclophilin A seems to be necessary for HIV-1 replication in primary T cells.

L13 ANSWER 6 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97089614 EMBASE
DOCUMENT NUMBER: 1997089614
TITLE: .alpha.1-adrenoceptor activation of a non-selective cation current in rabbit portal vein by 1,2-diacyl-sn-glycerol.
AUTHOR: Helliwell R.M.; Large W.A.
CORPORATE SOURCE: R.M. Helliwell, Dept Pharmacology Clin Pharmacology, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, United Kingdom. r.helliwell@sghms.ac.uk
SOURCE: Journal of Physiology, (1997) 499/2 (417-428).
Refs: 37
ISSN: 0022-3751 CODEN: JPHYA7
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 1. The transduction mechanisms involved in the activation and modulation of the noradrenaline-activated cation current (I(cat)) were investigated with whole-cell patch clamp techniques in rabbit portal vein smooth muscle cells. 2. Intracellular application of guanosine 5-O-(3-thiotriphosphate) (GTP.gamma.S, 500.mu.M) evoked a 'noisy' inward current at -50 mV with a similar current-voltage relationship and reversal potential to the current evoked by bath application of noradrenaline (100 .mu.M). Guanosine 5-O-(2-thiodiphosphate) (GDP.beta.S, 1 mM) markedly inhibited noradrenaline-activated I(cat). 3. The phospholipase C (PLC) inhibitor U73122 inhibited the amplitude of the noradrenaline-activated I(cat) in a concentration- and time-dependent manner and the IC50 was about 180 nM. U73122 had similar effects on the cation current evoked by GTP.gamma.S. 4. Intracellular application of myo-inositol 1,4,5-trisphosphate (IP3, 100 .mu.M) from the patch pipette did not activate any membrane current in cells where intracellular calcium concentration ([Ca2+](i)) was buffered to 14 nM, but subsequent addition of noradrenaline evoked I(cat). 5. Bath application of the 1,2-diacyl-sn-glycerol (DAG) analogue 1-oleoyl-2-acetyl-sn-glycerol (GAG, 10 .mu.M) activated I(cat), whereas the phorbol ester phorbol 12,13-dibutyrate (PDBu, 0.1-5 .mu.M) failed to activate I(cat), in every cell examined. I(cat) activated by GAG after bath application of PDBu was not significantly different from GAG-activated I(cat) in the absence of PDBu. The DAG lipase inhibitor RHC80267 (10 .mu.M) activated I(cat) in some cells, whereas the DAG kinase inhibitor R59949 (10 .mu.M) never activated I(cat). 6. Bath application of the protein kinase C inhibitor chelerythrine (1-10 .mu.m) had no effect on either OAG- or noradrenaline-activated I(cat). 7. It is concluded that noradrenaline activates I(cat) via a G-protein coupled to PLC and that the resulting DAG product plays a central role in the activation of cation channels via a protein kinase C-independent mechanism.

L13 ANSWER 7 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97086062 EMBASE
DOCUMENT NUMBER: 1997086062
TITLE: Protease inhibitors in patients with HIV disease. Clinically important pharmacokinetic considerations.
AUTHOR: Barry M.; Gibbons S.; Back D.; Mulcahy F.
CORPORATE SOURCE: Dr. M. Barry, Department Pharmacology Therapeutics, Ashton Street Medical School, University of Liverpool, Ashton Street, Liverpool L69 3GE, United Kingdom
SOURCE: Clinical Pharmacokinetics, (1997) 32/3 (194-209).
Refs: 124
ISSN: 0312-5963 CODEN: CPKNDH
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Since its introduction in 1987, zidovudine monotherapy has been the treatment of choice for patients with HIV infection. Unfortunately it has been established that the beneficial effects of zidovudine are not sustained due to the development of resistant viral strains. This has led to the strategy of combination therapy, and in 1995 treatment with zidovudine plus didanosine, or zidovudine plus zalcitabine, was demonstrated to be more effective than zidovudine monotherapy in preventing disease progression and reducing mortality in patients with HIV disease. Recent work demonstrates an even greater antiviral effect from triple therapy with 2 nucleosides, zidovudine plus zalcitabine with the addition of saquinavir, a new protease inhibitor drug. The HIV protease enzyme is responsible for the post-translational processing of gag and gag-pol polyprotein precursors, and its inhibition by drugs such as saquinavir, ritonavir, indinavir and VX-478 results in the production of non-infectious virions. As resistance may also develop to the protease inhibitors they may be used in combination, and future strategies may well include quadruple therapy with 2 nucleoside analogues plus 2 protease inhibitors. Administration of protease inhibitors alone or in combination with other drugs does raise a number of important pharmacokinetic issues for patients with HIV disease. Some protease inhibitors (e.g. saquinavir) have kinetic profiles characterised

by reduced absorption and a high first pass effect, resulting in poor bioavailability which may be improved by administrating with food. Physiological factors including achlorhydria, malabsorption and hepatic dysfunction may influence the bioavailability of protease inhibitors in HIV disease. Protease inhibitors are very highly bound to plasma **proteins** (> 98%), predominantly to .alpha.1-acid glycoprotein. This may influence their antiviral activity in vitro and may also predispose to plasma **protein** displacement interactions. Such interactions are usually only of clinical relevance if the metabolism of the displaced drug is also inhibited. This is precisely the situation likely to pertain to the protease inhibitors, as ritonavir may displace other protease inhibitor drugs, such as saquinavir, from plasma **proteins** and inhibit their metabolism. Protease inhibitors are extensively metabolised by the cytochrome P450 (CYP) enzymes present in the liver and small intestine. In vitro studies suggest that the most influential CYP isoenzyme involved in the metabolism of the protease inhibitors is CYP3A, with the isoforms CYP2C9 and CYP2D6 also contributing. Ritonavir has an elimination half-life (t(1/4.beta.)) of 3 hours, indinavir 2 hours and saquinavir between 7 and 12 hours. Renal elimination is not significant, with less than 5% of ritonavir and saquinavir excreted in the unchanged form. As patients with HIV disease are likely to be taking multiple prolonged drug regimens this may lead to drug interactions as a result of enzyme induction or inhibition. Recognised enzyme inducers of CYP3A, which are likely to be prescribed for patients with HIV disease, include rifampicin (rifampin) [treatment of pulmonary tuberculosis], rifabutin (treatment and prophylaxis of Mycobacterium avium complex), phenobarbital (phenobarbitone), phenytoin and carbamazepine (treatment of seizures secondary to cerebral toxoplasmosis or cerebral lymphoma). These drugs may reduce the plasma concentrations of the protease inhibitors and reduce their antiviral efficacy. If coadministered drugs are substrates for a common CYP enzyme, the elimination of one or both drugs may be impaired. Drugs which are metabolised by CYP3A and are likely to be used in the treatment of patients with HIV disease include the azole antifungals, macrolide antibiotics and dapsone; therefore, protease inhibitors may interact with these drugs. Although dapsone and cotrimoxazole (trimethoprim/sulfamethoxazole) are used in the treatment and prophylaxis of Pneumocystis carinii pneumonia, the incidence of adverse effects is very high, and has been attributed to the formation of a hydroxylamine metabolite mediated by CYP3A and CYP2C9 isoenzymes. The protease inhibitors, particularly ritonavir, may inhibit hydroxylamine production and reduce the incidence of adverse effects. This potential interaction may be beneficial and should be studied in the clinical setting. Protease inhibitors will be prescribed in combination with nucleoside **analogues**. It is unlikely that a pharmacokinetic drug interaction will result as the metabolic pathways differ. The effect of protease inhibitors on the intracellular phosphorylation of nucleoside **analogues** is unknown.

L13 ANSWER 8 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 5
ACCESSION NUMBER: 96372634 EMBASE
DOCUMENT NUMBER: 1996372634
TITLE: Identification of proteolytic cleavage sites within the **gag-analogue protein** of Ty1 virus-like particles.
AUTHOR: Martin-Rendon E.; Hurd D.W.; Marfany G.; Kingsman S.M.; Kingsman A.J.
CORPORATE SOURCE: Department of Biochemistry, University of Oxford, South Parks Road,Oxford OX1 3QU, United Kingdom
SOURCE: Molecular Microbiology, (1996) 22/5 (1035-1043). ISSN: 0950-382X CODEN: MOMIEE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Like retroviruses, the yeast retrotransposon Ty1 produces its proteins as precursors that are subsequently cleaved by a protease encoded by the element. These cleavage events are essential for transposition as they release the active reverse transcriptase and integrase and they modify the structure of the virus-like particles in a way that is analogous to the morphological changes that occur during retrovirus core maturation. Using a combination of epitope tagging, amino acid analysis and mutagenesis, we have identified the major cleavage sites for the Ty1 protease within the particle-forming protein, p1, at 407S/408N. In addition, we present evidence indicating that the Ty1 protease may be a 17 kDa protein.

L13 ANSWER 9 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96154145 EMBASE
DOCUMENT NUMBER: 1996154145
TITLE: Current knowledge and future prospects for the use of HIV protease inhibitors.
AUTHOR: Moyle G.; Gazzard B.
CORPORATE SOURCE: Kobler Centre, Chelsea and Westminster Hospital, 369 Fulham Rd,London SW10 9TH, United Kingdom
SOURCE: Drugs, (1996) 51/5 (701-712). ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The HIV protease (or **proteinase**) enzyme is an essential component of the replicative cycle of HIV, performing the post-transitional processing of the **gag** and **gag-pol** gene products into the functional core **proteins** and viral enzymes. Inhibition of this enzyme leads to production of immature noninfectious viral progeny, and hence prevention of further rounds of infection. Structurally, the enzyme is a homodimer consisting of two identical 99 amino acid chains. HIV protease is a member of the aspartic protease family but is structurally dissimilar to human aspartic proteases such as renin, gastricsin and cathepsin D and E, suggesting the possibility of creating inhibitors with a wide therapeutic index. At least 6 inhibitors of HIV protease are currently in clinical development: saquinavir, indinavir, ritonavir, nelfinavir (AG-1343), KNI-272 and VX-478, the first four of which have shown antiretroviral activity and acceptable tolerability in initial phase I/II clinical trials. Resistance or reduced sensitivity to the leading protease inhibitors has been reported in vivo and appears to be associated with loss of therapeutic effect. However, resistance patterns appear to be distinct. Treatment for 1 year with indinavir has been reported to lead to selection of virus in 4

patients, which was cross-resistant to all other leading protease inhibitors. On the other hand, a larger series of clinical isolates from patients receiving saquinavir alone or in combination with zidovudine for up to 3 years did not lead to virus cross-resistant to either indinavir or ritonavir. This suggests that care should be exercised in designing the sequence of protease usage. Additionally, differing resistance patterns may be used to select combinations of protease inhibitors in future trials. Data from studies combining protease inhibitors with nucleoside **analogues** suggest value in terms of larger and more prolonged virological and immunological marker responses than are observed with single agent therapy, and this is likely to be the primary role for protease inhibitors; both in initial combinations for patients commencing therapy and as add-in therapies for patients previously treated with antiretrovirals. However, in vitro and animal pharmacokinetic studies also give evidence of the possibility of combining protease inhibitors, potentially leading to improved bioavailability, antiviral synergy and delay in emergence of viral resistance.

L13 ANSWER 10 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 6
ACCESSION NUMBER: 96201151 EMBASE
DOCUMENT NUMBER: 1996201151
TITLE: Phorbol 12-myristate 13-acetate stimulates the release of glycosaminoglycans from cultured vascular endothelial cells: Possible involvement of protein kinase C activation.
AUTHOR: Fujii N.; Kaji T.; Yamamoto C.; Fujiwara Y.; Koizumi F.
CORPORATE SOURCE: Department of Environmental Science, Faculty of Pharmaceutical Sciences, Hokuriku University, Ho-3 Kanagawa-machi,Kanazawa 920-11, Japan
SOURCE: Thrombosis Research, (1996) 82/5 (379-387).
ISSN: 0049-3848 CODEN: THBRAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We investigated the release of glycosaminoglycans (**GAGs**) labeled with [3H]glucosamine and [35S]sulfate into the medium from cultured bovine aortic endothelial cells stimulated by phorbol 12-myristate 13-acetate (PMA) which is an activator of **protein** kinase C (PKC). The **GAG** release was significantly accelerated by PMA without an increase in the leakage of lactate dehydrogenase but was unchanged by 4.alpha.-phorbol 12,13-didecanoate which lacks the ability of PKC activation. The acceleration of **GAG** release by PMA was strongly suppressed by a PKC inhibitor H-7 but not by HA 1004 which is an inactive **analogue** of H-7. Characterization of **GAGs** released into the medium revealed that PMA increased both heparan sulfate and the other **GAGs** in a similar degree. Although the release of **GAGs** stimulated by thrombin was also suppressed by another PKC inhibitor staurosporine, stimulation by plasmin was unaffected by the inhibitor. The present data suggest that **protein** kinase C mediates the release of endothelial cell **GAGs** including anticoagulant heparan sulfate and the stimulation of the release by thrombin includes this mechanism.

L13 ANSWER 11 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 7
ACCESSION NUMBER: 95256319 EMBASE
DOCUMENT NUMBER: 1995256319
TITLE: Influence of monosaccharide derivatives on liver cell glycosaminoglycan synthesis: 3-deoxy-D-xylo-hexose (3-deoxy-D-galactose) and methyl (methyl 4-chloro-4-deoxy-.beta.-D-galactopyranoside) uronate.
AUTHOR: Thomas S.S.; Plenkiewicz J.; Ison E.R.; Bols M.; Zou W.; Szarek W.A.; Kisilevsky R.
CORPORATE SOURCE: Department of Pathology, Queen's University,Kingston, Ont. K7L 3N6, Canada
SOURCE: Biochimica et Biophysica Acta - Molecular Basis of Disease, (1995) 1272/1 (37-48).
ISSN: 0925-4439 CODEN: BBADEX
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
048 Gastroenterology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB An improved, convenient synthesis of 3-deoxy-D-xylo-hexose (3-deoxy-D-galactose) has been developed, and the chemical synthesis of a novel monosaccharide derivative, methyl (methyl 4-chloro-4-deoxy-.beta.-D-galactopyranosid)uronate (compound 10), is described. Using primary hepatocytes in culture, each was used to explore its effect on glycosaminoglycan (**GAG**) synthesis. In the absence of **analogues** hepatocytes synthesize primarily (92-95%) heparan sulphate. At 1 mM, 3-deoxy-D-galactose had little observable effect on either liver cell **GAG** or **protein** synthesis. At 10 mM and 20 mM, 3-deoxy-D-galactose reduced [3H]glucosamine and 35SO4 incorporation into hepatocyte cellular **GAGs** to, respectively, 75% and 60% of the control cells. This inhibition of **GAG** synthesis occurred without any effect on hepatocyte **protein** synthesis, indicating that 3-deoxy-D-galactose's effect on **GAG** synthesis is not mediated through an inhibition of proteoglycan core **protein** synthesis. Furthermore, **GAGs** in the presence of 20 mM of the **analogue** were significantly reduced in size, 17 kDa vs. 66 kDa in untreated cells. These results reflect either impaired cellular **GAG** chain elongation, and/or altered **GAG** chain degradation. Compound 10 exhibited a concentration-dependent inhibition of both hepatocyte cellular **GAG** and **protein** synthesis. At concentrations of 5, 10 and 20 mM, compound 10 inhibited **GAG** and **protein** synthesis by 20, 65 and 90%, respectively. Exogenous uridine was able to restore partially the inhibition of **protein** synthesis, but was unable to reverse the effect of compound 10 on **GAG** synthesis. These results show that part of the effect of compound 10 on **GAG** synthesis is not mediated by an inhibition of proteoglycan core **protein** synthesis. **GAGs** in the presence of compound 10 are half as large as those in the absence of this compound (33 and 66 kDa, respectively). These results again may reflect either impaired cellular **GAG** chain elongation and/or altered **GAG** chain degradation. Potential metabolic routes for each **analogue**'s effect are presented.

L13 ANSWER 12 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 8
ACCESSION NUMBER: 94357878 EMBASE
DOCUMENT NUMBER: 1994357878
TITLE: Functional association of cyclophilin A with HIV-1 virions.

AUTHOR: Thali M.; Bukovsky A.; Kondo E.; Rosenwirth B.; Walsh C.T.; Sodroski J.; Gottlinger H.G.
CORPORATE SOURCE: Division of Human Retrovirology, Dana-Farber Cancer Institute, Harvard Medical School,Boston, MA 02115, United States
SOURCE: Nature, (1994) 372/6504 (363-365).
ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cyclophilins are a family of **proteins** that bind the immunosuppressant cyclosporin A, possess peptidyl-prolyl cis-trans isomerase activity, and assist in the folding of **proteins**. Human cyclophilins A and B are host cell **proteins** that bind specifically to the HIV-1 **Gag** polyprotein p55(**gag**) in vitro. Here we report that viral particles formed by p55(**gag**), in contrast to particles formed by the **Gag** polyproteins of other retroviruses, contain significant amounts of cyclophilin A. Sequences in the capsid domain of p55(**gag**) are both required and sufficient for the virion-association of cyclophilin A. The association of cyclophilin A with HIV-1 virions was inhibited in a dose-dependent manner by cyclosporin A as well as by SDZ NIM811 ([Melle-4]cyclosporin), a non-immunosuppressive **analogue** of cyclosporin A. Drug-induced reductions in virion-associated cyclophilin A levels were accompanied by reductions in virion infectivity, indicating that the association is functionally relevant. Moreover, SDZ NIM811 inhibited the replication of HIV-1 but was inactive against SIV(MAC), a primate immunodeficiency virus closely related to HIV-1, which does not incorporate cyclophilin A.

L13 ANSWER 13 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94362824 EMBASE
DOCUMENT NUMBER: 1994362824
TITLE: Hypoxia and cobalt stimulate lactate dehydrogenase (LDH) activity in vascular smooth muscle cells.
AUTHOR: Marti H.H.; Jung H.H.; Pfeilschifter J.; Bauer C.
CORPORATE SOURCE: Physiologisches Institut, University Zurich-Irchel, Winterthurerstrasse 190,CH-8057 Zurich, Switzerland
SOURCE: Pflugers Archiv European Journal of Physiology, (1994) 429/2 (216-222).
ISSN: 0031-6768 CODEN: PFLABK
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB O2 plays a dominant role in the metabolism and viability of cells; changes in O2 supply lead to many physiological responses in the cell. Recent reports have shown that hypoxia induces the transcription of a number of genes, among them those for the glycolytic enzymes. We have investigated signalling events that may lead to enhanced activity of lactate dehydrogenase (LDH) in cultured vascular smooth muscle (VSM) cells derived from rat aorta, grown under hypoxic conditions (1% versus 20% O2). LDH was chosen because this enzyme exhibits one of the largest increases in activity among the glycolytic enzymes after hypoxic stimulation of cells. Hypoxic exposure of VSM cells for 24 h resulted in a 2-fold increase in LDH activity and in a 2.5-fold increase in intracellular cAMP levels. Agents that activate adenylate cyclase, such as forskolin, cholera toxin and 1-methyl-3-isobutylxanthine (IBMX), and thus increase cAMP production, significantly induced LDH activity. Moreover, induction of LDH activity by hypoxia was prevented in the presence of the **protein** kinase A inhibitor N-[2-(methyl-amino)ethyl]-5-isoquinolinsulphon amide dihydrochloride (H-8), and the cyclooxygenase inhibitor indomethacin. In contrast to the cAMP-stimulating agents, stable cGMP **analogues** (dibutyryl-cGMP, 8-bromo-cGMP), activators of **protein** kinase C [12-O- tetradecanoylphorbol-13-acetate (TPA), and 1-oleoyl-2-acetyl-glycerol (GAG), and the calcium ionophore ionomycin did not alter LDH activity in VSM cells kept at 20% O2. A dose-dependent increase in LDH activity was also observed in normoxic cells exposed to cobalt chloride (50-200 .mu.M), indicating that a metal binding **protein** might be involved in this signalling cascade. This transition metal does not seem to act by interfering with cellular oxidative phosphorylation, because 10-5-10-4 M cyanide, a potent inhibitor of cell respiration, had no effect on;LDH activity, as has been also shown for the production of erythropoietin (EPO). Thus, we suggest that the phosphorylation potential is not crucial to the O2- sensing mechanism regulating LDH activity and EPO production. Our results suggest that the 'metabolic indicator' leading to an enhanced LDH activity under hypoxic conditions in VSM cells is represented by cAMP.

L13 ANSWER 14 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 9
ACCESSION NUMBER: 93212454 EMBASE
DOCUMENT NUMBER: 1993212454
TITLE: A survey of synthetic HIV-1 peptides with natural and chimeric sequences for differential reactivity with Zimbabwean, Tanzanian and Swedish HIV-1-positive sera.
AUTHOR: Blomberg J.; Lawoko A.; Pipkorn R.; Moyo S.; Malmvall B.E.; Shao J.; Dash R.; Tswana S.
CORPORATE SOURCE: Section of Virology, Department of Medical Microbiology, University of Lund, Solvegaten 23,S-223 62 Lund, Sweden
SOURCE: AIDS, (1993) 7/6 (759-767).
ISSN: 0269-9370 CODEN: AIDSET
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
017 Public Health, Social Medicine and Epidemiology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective: To determine whether the known sequence differences between African and non-African HIV-1 strains are reflected in the serological response. Design and methods: We investigated the antibody reactivity of 34 Swedish, 30 Tanzanian and 42 Zimbabwean HIV-1-positive sera to 67 synthetic **peptides** with sequences from North American and African HIV-1 isolates, mostly derived from regions of **gag** and env known to be antigenic. Not all sera were tested against all **peptides**. Results: Differences in frequency of reactivity were noted with **peptides** covering the entire third variable domain (V3), which is a primary neutralization determinant, and the carboxyl terminus of gp120, in two regions of gp41, and the carboxyl terminus of

p24. In env Tanzanian sera reacted preferentially with a V3 **peptide** from the strain JY1 (Zaire). Gradual substitutions in the central motif in V3 of ELI from GLGQ to GPGR, typical of many non-African strains, led to a gradual increase in reactivity of many Swedish sera, but did not affect Tanzanian and Zimbabwean sera, suggesting that the major epitopes recognized by these African sera are outside GPGR. V3 **peptides** from the MN and Z3 strains reacted with most sera, but missed 30% of those of Tanzanian origin. In the carboxyl terminus of gp120 both sets of African sera reacted preferentially with **peptides** from strains JY1 and MAL. Swedish sera reacted strongest with **analogues** from strains Z321 and HXB2. In gp41, Swedish sera showed a weak preference for reactivity with HXB2-derived **peptides** in the immunodominant region (amino acids 590-620), and further towards the carboxyl terminus (amino acids 620-665). Conclusion: The differences in serological reactivity were as great between Zimbabwe and Tanzania as between the two African sets and the Swedish. The geographical differences in the pattern of reactivity with HIV **peptides** probably depend on both host and viral variation and may be developed into a seroepidemiological tool, useful for optimization of future HIV vaccines.

L13 ANSWER 15 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 10
ACCESSION NUMBER: 94022461 EMBASE
DOCUMENT NUMBER: 1994022461
TITLE: Effects of beraprost sodium, a stable analogue of prostacyclin, on hyperplasia, hypertrophy and glycosaminoglycan synthesis of rat aortic smooth muscle cells.
AUTHOR: Koh E.; Morimoto S.; Jiang B.; Inoue T.; Nabata T.; Kitano S.; Yasuda O.; Fukuo K.; Ogihara T.
CORPORATE SOURCE: Department of Geriatric Medicine, Osaka University Medical School, 2-2 Yamadaoka,Suita, Osaka 553, Japan
SOURCE: Artery, (1993) 20/5 (242-252).
ISSN: 0098-6127 CODEN: ARTEDR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The effects of beraprost sodium, a stable **analogue** of prostacyclin, on the syntheses of DNA, **protein** and glycosaminoglycans (**GAG**) of cultured vascular smooth muscle cells (SMC) were studied. SMC were isolated from the thoracic aorta of male Wistar rats. The syntheses of DNA, **protein** and **GAG** of SMC were determined by incorporations of [3H]thymidine, [3H]leucine and [35S]sulfuric acid, respectively. Insulin at a concentration of 10-6 M stimulated DNA synthesis 4 fold compared to control. Beraprost sodium suppressed the insulin-stimulated DNA synthesis dose-dependently at concentrations greater than 10-7 M and suppressed it by 68% at 10-5 M. Platelet derived growth factor (PDGF) at a concentration of 20 ng/ml stimulated DNA synthesis 6 fold compared to control. Beraprost sodium suppressed the PDGF-stimulated DNA synthesis dose-dependently at concentrations greater than 10-7 M and suppressed it by 51% at 10-5 M. Beraprost sodium suppressed **GAG** synthesis dose-dependently at concentrations greater than 10-7 M and suppressed it by 49% at 10-5 M. However, beraprost sodium at concentrations up to 10-5 M did not affect **protein** synthesis. These results indicate that beraprost sodium suppressed the proliferation and **GAG** synthesis of SMC but did not affect hypertrophy. Beraprost sodium may be a potent antiarteriosclerotic agent through suppression of hyperplasia of SMC and modification of matrix **protein**.

L13 ANSWER 16 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 11
ACCESSION NUMBER: 93088179 EMBASE
DOCUMENT NUMBER: 1993088179
TITLE: Mechanism of inhibition of the retroviral protease by a Rous sarcoma virus peptide substrate representing the cleavage site between the gag p2 and p10 proteins.
AUTHOR: Cameron C.E.; Grinde B.; Jentoft J.; Leis J.; Weber I.T.; Copeland T.D.; Wlodawer A.
CORPORATE SOURCE: Dept. of Biochemistry, Case Western Reserve Univ. Med. Sch., 2119 Abington Rd.,Cleveland, OH 44106-4935, United States
SOURCE: Journal of Biological Chemistry, (1992) 267/33 (23735-23741).
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The activity of the avian myeloblastosis virus (AMV) or the human immunodeficiency virus type 1 (HIV-1) protease on **peptide** substrates which represent cleavage sites found in the **gag** and **gag**-pol polyproteins of Rous sarcoma virus (RSV) and HIV-1 has been analyzed. Each protease efficiently processed cleavage site substrates found in their cognate polyprotein precursors. Additionally, in some instances heterologous activity was detected. The catalytic efficiency of the RSV protease on cognate substrates varied by as much as 30-fold. The least efficiently processed substrate, p2- p10, represents the cleavage site between the RSV p2 and p10 **proteins**. This **peptide** was inhibitory to the AMV as well as the HIV-1 and HIV-2 protease cleavage of other substrate **peptides** with K(i) values in the 5-20 .mu.M range. Molecular modeling of the RSV protease with the p2-p10 **peptide** docked in the substrate binding pocket and analysis of a series of single-amino acid- substituted p2-p10 **peptide analogues** suggested that this **peptide** is inhibitory because of the potential of a serine residue in the P1' position to interact with one of the catalytic aspartic acid residues. To open the binding pocket and allow rotational freedom for the serine in P1', there is a further requirement for either a glycine or a polar residue in P2' and/or a large amino acid residue in P3'. The amino acid residues in P1-P4 provide interactions for tight binding of the **peptide** in the substrate binding pocket.

L13 ANSWER 17 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 12
ACCESSION NUMBER: 92337478 EMBASE
DOCUMENT NUMBER: 1992337478
TITLE: Synthesis of stereochemically defined phosphonamidate-containing peptides: Inhibitors for the HIV-1 proteinase.
AUTHOR: Camp N.P.; Hawkins P.C.D.; Hitchcock P.B.; Gani D.
CORPORATE SOURCE: Chemistry Department, University of St. Andrews,St.

Andrews, Fife KY16 9ST, United Kingdom
SOURCE: Bioorganic and Medicinal Chemistry Letters, (1992) 2/9 (1047-1052).
ISSN: 0960-894X CODEN: BMCLE8
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Phosphonamidate-containing peptidic substrate **analogues** of the HIV-1 **gag**-pol **proteinase**-reverse transcriptase junction {-Phe-.PSI.[PO2-N]-(S)-Pro and -Phe-.PSI.[P(OMe)O-N]-(S)-Pro-}, mimicks for the transition states for proteolysis, have been synthesised. The absolute stereochemistry at C-1 of the phosphonophenylalanine residue was determined by X-ray crystallography. Boc-(S)-Asn-Phe-.PSI.[PO2-N]-(S)-Pro-(S)-Ile-NH-i-Bu and Boc-(S)-Asn-(R)-Phe-.PSI.[P(OMe)O-N]-(S)-Pro-(S)-Ile-NH-i-Bu inhibit the HIV-1 **proteinase**.

L13 ANSWER 18 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 13
ACCESSION NUMBER: 93007882 EMBASE
DOCUMENT NUMBER: 1993007882
TITLE: Inhibition of HIV by an anti-HIV protease synthetic peptide blocks an early step of viral replication.
AUTHOR: Venaud S.; Yahi N.; Fehrentz J.L.; Guettari N.; Hirsch I.; Nisato D.; Chermann J.C.
CORPORATE SOURCE: Unite de Recherches INSERM sur, les Retrovirus et Maladies Associees, Campus de Luminy, BP 33,13273 Marseille Cedex 9, France
SOURCE: Research in Virology, (1992) 143/5 (311-319).
ISSN: 0923-2516 CODEN: RESVEY
COUNTRY: France
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; French
AB The processing of the human immunodeficiency virus (HIV) **gag** and **gag**-pol precursor **proteins** by the virus-encoded protease is an essential step in maturation of infectious virus particles. Like most retroviral proteases, the HIV protease belongs to the aspartyl-protease family and can be inhibited by specific inhibitors. Twenty-four synthetic **peptides** known to be inhibitors of human renin were tested for inhibition of HIV replication in tissue cultures. One of them, a synthetic **peptide analogue**, SR41476, which has been shown to be a specific inhibitor of purified recombinant HIV1 protease in vitro, totally blocked infection with different isolates including the HIV1 LAV prototype, the highly cytopathic Zairian isolate HIV1 NDK, and HIV2 ROD, both in primary blood lymphocytes (PBL) and in the lymphoid cell lines MT4 and CEM, for at least 3 weeks. It also significantly reduced virus replication in chronically infected CEM cells, without any effect on cell proliferation. Radioimmunoprecipitation assay revealed that the inhibitor blocked processing of polyprotein precursors p55 **gag** and p40 **gag** into a mature form of **gag proteins**, p25 and p18. Synthetic **peptide analogue** SR 41476, when added before infection, efficiently inhibited formation of HIV DNA provirus and successfully suppressed synthesis of HIV-specific **proteins**. These results imply that the HIV protease inhibitor not only inhibited virus maturation in the late phase of the HIV replication cycle, but also interfered in the early phase, before the provirus was formed. This mechanism of antiviral activity provides new possibilities and strategies for AIDS chemotherapy.

L13 ANSWER 19 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92124285 EMBASE
DOCUMENT NUMBER: 1992124285
TITLE: Signal transduction in glycosaminoglycan (GAG) synthesis by cultured chondrocytes and its inhibition by inflammatory cell-derived hydrogen peroxide.
AUTHOR: Matsubara T.; Kimura T.; Kuroda T.; Hirohata K.
CORPORATE SOURCE: Department of Orthopaedic Surg, Kobe University School of Medi, 7 Chome Kusunoki-cho,Chuo-ku, Kobe, Japan
SOURCE: British Journal of Rheumatology, (1992) 31/4 SUPPL. (27-32).
ISSN: 0263-7103 CODEN: BJRHDF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Signal transduction in glycosaminoglycan (**GAG**) synthesis by chondrocytes has been studied. The activity of various subspecies of **protein** kinase C (PKC) in chondrocytes derived from rodent costal cartilage and bovine articular cartilage has been determined and the role of PKC in **GAG** synthesis as well as the possible interactions of PKC with calcium- or cyclic AMP (cAMP)-dependent systems in the synthesis of **GAG**. To investigate **GAG** synthesis in inflammatory conditions, the effects of hydrogen peroxide on PKC activity of the chondrocytes and PKC-mediate **GAG** synthesis have been studied. 12-O-tetradecanoylphorbol-13-acetate (TPA), an activator of PKC, increased **GAG** synthesis in a dose-dependent fashion. This suggests that PKC up-regulates the synthesis of **GAG** in cultured chondrocytes. This increase was not significantly affected by simultaneous addition of the calcium ionophore, ionomycin, or dibutyryl cAMP (db-cAMP), a cAMP **analogue**. Ionomycin and db-cAMP, when used alone, did not significantly alter **GAG** synthesis by chondrocytes. Thus there appears to be no interaction between PKC and calcium- or cAMP-mediated systems in **GAG** synthesis. The increase in **GAG** synthesis induced by TPA was significantly ($P<0.01$) reduced by simultaneous addition of hydrogen peroxide (10-6 M), without affecting cell viability. The activity of PKC in chondrocytes pretreated with 10-6 M hydrogen peroxide was also significantly inhibited. Thus hydrogen peroxide which is generated by inflammatory cells may be important in suppression of **GAG** synthesis in inflammatory conditions.

L13 ANSWER 20 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91321861 EMBASE
DOCUMENT NUMBER: 1991321861
TITLE: Purification and biochemical characterization of

recombinant simian immunodeficiency virus protease and comparison to human immunodeficiency virus type 1 protease.
AUTHOR: Grant S.K.; Deckman I.C.; Minnich M.D.; Culp J.; Franklin S.; Dreyer G.B.; Tomaszek Jr. T.A.; Debouck C.; Meek T.D.
CORPORATE SOURCE: Dept. of Medicinal Chemistry, SmithKline Beecham, Pharmaceuticals, 709 Swedeland Road,King of Prussia, PA 19406, United States
SOURCE: Biochemistry, (1991) 30/34 (8424-8434).
ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Simian immunodeficiency virus protease (SIV-PR) was produced in Escherichia coli with a recombinant expression system in which the mature enzyme autoprocessed from a precursor form. Recombinant SIV and HIV-1 (human immunodeficiency virus, type 1) proteases were purified from bacterial cell lysates by use of sequential steps of ammonium sulfate precipitation and size-exclusion and ion-exchange chromatography. The amino acid composition, amino-terminal sequence, and molecular weight (monomer) of the recombinant SIV-PR were in accord with that of the 99 amino acid polypeptide predicted from the SIV(Mac)-PR nucleotide sequence. The active form of SIV-PR was shown to be dimeric by gel filtration chromatography. Inhibition by pepstatin A, time-dependent inactivation by 1,2-epoxy-3-(4-nitrophenoxy)propane, and pH rate profiles using oligopeptide substrates demonstrated that SIV-PR behaves as an aspartic protease. Recombinant HIV-1 Pr55(gag) precursor was processed in vitro by SIV-PR and HIV-1 PR with indistinguishable proteolytic patterns upon NaDodSO4-polyacrylamide gel electrophoresis. Oligopeptide substrates for HIV-1 PR were found to be suitable substrates for recombinant SIV-PR with the exception of a **peptide** containing the site identified for p66/p51 cleavage (Phe*Tyr) within HIV-1 reverse transcriptase (RT). Several synthetic **peptide analogue** inhibitors of HIV-1 PR were also potent inhibitors of SIV-PR, indicating that SIV infection in macaques and rhesus monkeys should be useful models for the preclinical evaluation of acquired immunodeficiency syndrome (AIDS) therapeutics targeted toward the virally encoded HIV-1 protease.

L13 ANSWER 21 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 14
ACCESSION NUMBER: 91284073 EMBASE
DOCUMENT NUMBER: 1991284073
TITLE: Evidence for a ''Cysteine-Histidine box'' metal-binding site in an Escherichia coli aminoacyl-tRNA synthetase.
AUTHOR: Miller W.T.; Hill K.A.W.; Schimmel P.
CORPORATE SOURCE: Dept. of Biology, Massachusetts Inst. of Technol,Cambridge, MA 02139, United States
SOURCE: Biochemistry, (1991) 30/28 (6970-6976).
ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Escherichia coli alanyl-tRNA synthetase contains the sequence Cys-X2-Cys-X6-His-X2-His. This motif is distinct from the zinc fingers of DNA-binding **proteins** but has some similarity to the Cys-X2-Cys-X4-His-X4-Cys zinc-binding motif of retroviral **gag proteins**, where it has a role in RNA packaging. In Ala-tRNA synthetase, this sequence is located in an amino-terminal domain which has the site for docking the acceptor end of the tRNA near the bound aminoacyl adenylate and is immediately adjacent in the sequence to the location of a mutation that affects the specificity of tRNA recognition. We show here that Ala-tRNA synthetase contains approximately 1 mol of zinc/mol of polypeptide and that addition of the zinc chelator 1,10-phenanthroline inhibits its aminoacylation activity. Conservative mutations of specific cysteine or histidine residues in the ''Cys-His box'' destabilize and inactivate the enzyme, whereas mutations of intervening amino acids do not inactivate. The possibility that this motif can bind zinc (or cobalt) was demonstrated with a synthetic 22 amino acid **peptide** that is based on the sequence of the alanine enzyme. The **peptide**-cobalt complex has the spectral characteristics of tetrahedral coordination geometry. The results establish that the Cys-His box motif of Ala-tRNA synthetase has the potential to form a specific complex with zinc (at least in the context of a synthetic **peptide analogue**) and suggest that this motif is important for enzyme stability/activity.

L13 ANSWER 22 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 15
ACCESSION NUMBER: 91185841 EMBASE
DOCUMENT NUMBER: 1991185841
TITLE: Antibodies to gp41 and nef in otherwise HIV-negative homosexual man with Kaposi's sarcoma.
AUTHOR: Bowden F.J.; McPhee D.A.; Deacon N.J.; Cumming S.A.; Doherty R.R.; Sonza S.; Lucas C.R.; Crowe S.M.
CORPORATE SOURCE: Macfarlane Burnet Centre, Medical Research, Yarra Bend Road,Fairfield, Vic. 3078, Australia
SOURCE: Lancet, (1991) 337/8753 (1313-1314).
ISSN: 0140-6736 CODEN: LANCAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A homosexual man with histologically confirmed Kaposi's sarcoma remained seronegative for HIV-1, HIV-2, and HTLV-I on conventional tests over a 4-year period. HIV cultures were also negative on thirteen separate occasions. However, serum antibodies to synthetic **peptide analogues** of the gp41 and **nef** regions of HIV-1 were consistently detected on an enzyme immunoassay. Tests with the polymerase chain reaction with primers directed to the **gag** and env regions were negative. The antigens to which the antibodies were produced might have come from a defective HIV mutant, another retrovirus, or a hitherto unknown 'agent of Kaposi's sarcoma' with similar antigenic epitopes.

L13 ANSWER 23 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 16
ACCESSION NUMBER: 92066148 EMBASE
DOCUMENT NUMBER: 1992066148
TITLE: Investigation of the role of metalloproteinases in recombinant human interleukin-1.beta.-induced degradation of rat femoral head cartilage.
AUTHOR: Seed M.P.; Thomson T.A.; Gardner C.R.
CORPORATE SOURCE: Dep of Experimental Pathology, William Harvey Research Inst, St Bartholomews Hosp Med Coll, Charter House

Square,London EC1M 6BQ, United Kingdom
SOURCE: Drugs under Experimental and Clinical Research, (1991) 17/7 (355-361).
ISSN: 0378-6501 CODEN: DECRDP
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The mechanism of proteoglycan (GAG) loss from rat femoral articular cartilage (FHC) induced by recombinant human interleukin-1.beta. (rhIL-1.beta.) in vitro has been investigated. The metalloproteinase inhibitor 1,10-phenanthroline, the serine proteinase inhibitor N.alpha.-p-tosyl-l-lysine chloromethyl ketone (TLCK), the activator of latent metalloproteinase p-aminophenylmercuric acid (APMA), and an inhibitory metalloproteinase substrate analogue U27391 were tested for their ability to modulate rhIL-1.beta. induced GAG loss and GAG synthesis ([35S]O4 uptake) inhibition. As expected 1,10-phenanthroline inhibited GAG loss, however [35S]O4 incorporation was significantly reduced. TLCK was without effect, and APMA inhibited both parameters. U27391 reversed both the inhibition of [35S]O4 incorporation and GAG loss. It is concluded that the adverse effects on proteoglycan metabolism explain the inhibitory actions of 1,10-phenanthroline and APMA, whilst the action of TLCK may indicate that serine proteinases are not involved in the activation of latent metalloproteinase. U27391 exhibited chondroprotective activity and confirmed the induction of either metalloproteinases such as stromelysin or collagenase by rhIL-1.beta. .

L13 ANSWER 24 OF 41 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:45773 BIOSIS
DOCUMENT NUMBER: BA93:25748
TITLE: ANALYSIS OF NON-INFECTIOUS HIV PARTICLES PRODUCED IN PRESENCE OF HIV PROTEINASE INHIBITOR.
AUTHOR(S): SCHAETZL H; GELDERBLOM T R; NITSCHKO H; VON DER HELM K
CORPORATE SOURCE: MAX-VON-PETTENKOFER-INSTITUT, UNIVERSITAET MUENCHEN, PETTENKOFER-STRASSE 9A, D-W-8000 MUNICH 2, GERMANY.
SOURCE: ARCH VIROL, (1991) 120 (1-2), 71-82.
CODEN: ARVIDF. ISSN: 0304-8608.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Newly developed substrate analogue peptidomimetics are able to inhibit the human immunodeficiency virus, HIV-1 proteinase at nanomolar concentration. In HIV infected cell culture they exhibit antiviral activity. We have analyzed the non-infectious HIV particles produced in chronically HIV infected cell culture in presence of one of these inhibitors. The total production of virus particles was not substantially reduced in drug treated cultures, compared to non-inhibited control cultures, but the infectivity of these virus particles was reduced about 100 fold. The processing of gag and gag -pol protein precursor was inhibited; only borderline activity of reverse transcriptase (RT) could be detected in these particles and they contained nonprocessed gag precursor protein.
Thin section electron microscopy of inhibitor-treated, HIV-infected cells revealed reduced viral cytopathogenicity and both inhibition of particle assembly and incomplete maturation of the particles formed. The HIV particles produced in the presence of the proteinase inhibitor were studded with envelope glycoprotein knobs and often comprised multiple budding regions, but were morphologically immature.

L13 ANSWER 25 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 17
ACCESSION NUMBER: 91049671 EMBASE
DOCUMENT NUMBER: 1991049671
TITLE: Reconstitution of constitutive secretion using semi-intact cells: Regulation by GTP but not calcium.
AUTHOR: Miller S.G.; Moore H.-P.H.
CORPORATE SOURCE: Division of Cell and Developmental Biology, Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720, United States
SOURCE: Journal of Cell Biology, (1991) 112/1 (39-54).
ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Regulated exocytosis in many permeabilized cells can be triggered by calcium and nonhydrolyzable GTP analogues. Here we examine the role of these effectors in exocytosis of constitutive vesicles using a system that reconstitutes transport between the trans-Golgi region and the plasma membrane. Transport is assayed by two independent methods: the movement of a transmembrane glycoprotein (vesicular stomatitis virus glycoprotein [VSV G protein]) to the cell surface; and the release of a soluble marker, sulfated glycosaminoglycan (GAG) chains, that have been synthesized and radiolabeled in the trans-Golgi. The plasma membrane of CHO cells was selectively perforated with the bacterial cytolysin streptolysin-O. These perforated cells allow exchange of ions and cytosolic proteins but retain intracellular organelles and transport vesicles. Incubation of the semi-intact cells with ATP and a cytosolic fraction results in transport of VSV G protein and GAG chains to the cell surface. The transport reaction is temperature dependent, requires hydrolyzable ATP, and is inhibited by N-ethylmaleimide. Non-hydrolyzable GTP analogs such as GTP.gamma.S, which stimulate the fusion of regulated secretory granules, completely abolish constitutive secretion. The rate and extent of constitutive transport between the trans-Golgi and the plasma membrane is independent of free Ca2+ concentrations. This is in marked contrast to fusion of regulated seretory granules with the plasma membrane, and transport between the ER and the cis-Golgi.

L13 ANSWER 26 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 18
ACCESSION NUMBER: 91331428 EMBASE
DOCUMENT NUMBER: 1991331428
TITLE: HIV-1 proteinase is required for synthesis of pro-viral DNA.
AUTHOR: Baboonian C.; Dalgleish A.; Bountiff L.; Gross J.; Oroszlan S.; Rickett G.; Smith-Burchnell C.; Troke P.; Merson J.
CORPORATE SOURCE: Pfizer Central Research,Sandwich, Kent, CT13 9NJ, United Kingdom

SOURCE: Biochemical and Biophysical Research Communications, (1991) 179/1 (17-24).
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB HIV-1 **proteinase** activity is thought to occur primarily post-integration by cleaving the viral Gag and Gag-Pol polyproteins. Its role in the pre-integration stages of viral replication, however, has not been studied in detail. Here we report that a synthetic **peptide analogue**, UK-88,947, which is a specific inhibitor of purified HIV-1 **proteinase**, inhibits the processing of the viral polyproteins in cultures of HIV-1 infected cells and prevents the formation of mature, infectious virions. Analysis of DNA from HIV-1 infected cells treated with UK-88,947 showed that viral DNA synthesis was inhibited when the compound was added to cultures one hour before infection. Similar results were obtained when AZT was used. Neither HIV-1 reverse transcriptase or the replication of FIV are inhibited by UK-88,947.

L13 ANSWER 27 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 90259916 EMBASE
DOCUMENT NUMBER: 1990259916
TITLE: Evidence for involvement of the protein kinase C pathway in the activation of p37(v-mos) protein kinase.
AUTHOR: Al-Bagdadi F.; Singh B.; Arlinghaus R.B.
CORPORATE SOURCE: Dept. of Molecular Pathology, University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd.,Houston, TX 77030, United States
SOURCE: Oncogene, (1990) 5/8 (1251-1257).
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Protein** kinases are known to undergo phosphorylation to regulate their activity. To determine whether the **protein** kinase activity of p37(v-mos) was similarly regulated, we investigated the influence of two well known **protein** kinases, namely **protein** kinase C and **protein** kinase A, on the activity of p37(v-mos) in vivo. NIH3T3 cells chronically transformed with Moloney murine sarcoma virus 124 were treated with high concentrations (200-400 nM) of phorbol 12-myristate 13-acetate (PMA) for 24-48 h, concentrations known to result in the total loss of **protein** kinase C by causing its translocation from the cytosol to cell membranes where it is downregulated. PMA treatment caused a drastic decrease in the **protein** kinase activity of p37(v-mos) without affecting its steady state level. Similar results were obtained with p85(gag-mos) expressed in ts110 Mo-MuSV transformed NRK cells. COntrol treatment with an inactive **analogue** of PMA, 4-.alpha. phorbol 12,13-didecanoate, had no effect on the p37(v-mos) **protein** kinase activity. Treatment of cells with a direct chemical inhibitor of **protein** kinase C, H-7 (1-(5-isoquinoline sulfonyl)-2-methylpiperazine dihydrochloride), approximately halved p37(v-mos) kinase activity, although the drug did not inhibit p37(v-mos) kinase activity directly in vitro. In contrast to the PMA effect, in vivo activation of **protein** kinase A by 8-(4-chlorophenylthio)-adenosine 3',5' cyclic monophosphate did not affect p37(v-mos) **protein** kinase activity levels. These findings indicate that the **protein** kinase C pathway but not the **protein** kinase A pathway modulates v-mos **protein** kinase activity.

L13 ANSWER 28 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 19
ACCESSION NUMBER: 90348024 EMBASE
DOCUMENT NUMBER: 1990348024
TITLE: An HIV-1 and HIV-2 cross-reactive cytotoxic T-cell epitope.
AUTHOR: Nixon D.F.; Huet S.; Rothbard J.; Kieny M.-P.; Delchambre M.; Thiriart C.; Rizza C.R.; Gotch F.M.; McMichael A.J.
CORPORATE SOURCE: Molecular Immunology Group, Inst. of Molecular Medicine, John Radcliffe Hospital,Oxford OX3 9DU, United Kingdom
SOURCE: AIDS, (1990) 4/9 (841-845).
ISSN: 0269-9370 CODEN: AIDSET
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
047 Virology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The HLA-B27-restricted HIV **gag** cytotoxic T-lymphocyte (CTL) epitope, 265-279, is highly conserved amongst HIV-1 isolates, only one, HIV-1(ELI), having a single amino acid substitution. Over the same region HIV-2 differs by five amino acids. As a broadly cross-protective AIDS vaccine should protect against infection from all isolates of HIV-1 and HIV-2, we tested CTL specific for the HIV-1 265-279 epitope with **peptide analogues** from HIV-1(ELI), HIV-2 and two simian immunodeficiency virus (SIV) isolates, and with recombinant vaccinia viruses expressing the respective **gag** genes, to determine whether there was any cross-reactivity for this CTL epitope. CTL from the HIV-1-infected donor could recognize the HIV-1(ELI) **peptide**, the HIV-2 **peptide** and recombinant vaccinia virus-infected target and one of the two SIV **peptide**-treated targets. Epitopes that exhibit such cross-activity may be valuable in vaccine design.

L13 ANSWER 29 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 20
ACCESSION NUMBER: 90034078 EMBASE
DOCUMENT NUMBER: 1990034078
TITLE: Substrate analogue inhibition and active site titration of purified recombinant HIV-1 protease.
AUTHOR: Tomasselli A.G.; Olsen M.K.; Hui J.O.; Staples D.J.; Sawyer T.K.; Heinrikson R.L.; Tomich C.-S.C.
CORPORATE SOURCE: Biopolymer Chemistry Res. Unit, The Upjohn Company,Kalamazoo, MI 49001, United States
SOURCE: Biochemistry, (1990) 29/1 (264-269).
ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 047 Virology
LANGUAGE: English

SUMMARY LANGUAGE: English

AB The aspartyl protease of human immunodeficiency virus 1 (HIV-1) has been expressed in Escherichia coli at high levels, resulting in the formation of inclusion bodies which contain denatured insoluble aggregates of the protease. After solubilization of these inclusion bodies in guanidinium chloride, the protease was purified to apparent homogeneity by a single-step reverse-phase HPLC procedure. The purified, but inactive, protein was denatured in 8 M urea and refolded to produce the active protease. Enzyme activity was demonstrated against the substrate H-Val-Ser-Gln-Asn-Tyr-Pro-Ile-Val-OH, modeled after the cleavage region between residues 128 and 135 in the HIV gag polyprotein. With this substrate, a V(max) of 1.3 .+-. 0.2 .mu.mol/(min.cntdot.mg) and K(M) of 2.0 .+-. 0.3 mM were determined at pH 5.5. Pepstatin (Iva-Val-Val-Sta-Ala-Sta-OH) and substrate **analogues** with the Tyr-Pro residues substituted by Sta, by Phe.PSI.[CH2N]Pro, and by Leu.PSI.(CH(OH)CH2)Val inhibited the protease with K(I) values of 360 nM, 3690 nM, 3520 nM, and <10 nM, respectively. All were competitive inhibitors, and the tightest binding compound provided an active site titrant for the quantitative determination of enzymatically active HIV-1 protease.

L13 ANSWER 30 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 90036706 EMBASE
DOCUMENT NUMBER: 1990036706
TITLE: Inhibition of HIV-1 protease in infected T-lymphocytes by synthetic peptide analogues.
AUTHOR: Meek T.D.; Lambert D.M.; Dreyer G.B.; Carr T.J.; Tomaszek Jr. T.A.; Moore M.L.; Strickler J.E.; Debouck C.; Hyland L.J.; Matthews T.J.; Metcalf B.W.; Petteway S.R.
CORPORATE SOURCE: Department of Medicinal Chemistry, Smith Kline and French Laboratories, 709 Swedeland Road, King of Prussia, PA 19406, United States
SOURCE: Nature, (1990) 343/6253 (90-92).
ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 047 Virology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The gag and pol genes of the human immunodeficiency virus type 1 (HIV-1) are translated as two polyproteins, Pr55(gag) and Pr160(gag-pol), which are subsequently cleaved by the action of a virus-encoded protease into the four structural **gag proteins** of the virion core (p17, p24, p7 and p6) and the pol-encoded enzymes essential for retrovirus replication (protease, reverse transcriptase, ribonuclease H, and endonuclease). Mutational inactivation of the proteases of HIV-1 and other retroviruses results in immature, non-infectious virions, indicating that exogenous inhibition of the protease may represent an attractive approach to anti-AIDS therapy. Here we demonstrate that synthetic **peptide analogues**, which are potent inhibitors of purified HIV-1 protease, inhibit the processing of the viral polyproteins in cultures of HIV-1-infected T lymphocytes and attenuate viral infectivity.

L13 ANSWER 31 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 90031055 EMBASE
DOCUMENT NUMBER: 1990031055
TITLE: Inhibition of human immunodeficiency virus 1 protease in vitro: Rational design of substrate analogue inhibitors.
AUTHOR: Dreyer G.B.; Metcalf B.W.; Tomaszek Jr. T.A.; Carr T.J.; Chandler III A.C.; Hyland L.; Fakhoury S.A.; Magaard V.W.; Moore M.L.; Strickler J.E.; Debouck C.; Meek T.D.
CORPORATE SOURCE: Dept.of Medicinal Chemistry, SKF Laboratories, P.O. Box 1539,King of Prussia, PA 19406-0939, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1989) 86/24 (9752-9756).
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 047 Virology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Inhibitors of the protease from human immunodeficiency virus 1 (HIV-1) were designed, synthesized, and kinetically characterized. **Analogues** of a heptapeptide substrate of HIV-1 protease with sequence similar to the p17-p24 cleavage site in the natural substrate, Pr55(gag), were synthesized in which the scissile dipeptide bond was replaced with bonds from six categories of stable mimics of an aspartic proteolysis transition state or intermediate. These mimics included an **analogue** of statine, hydroxyethylene isosteres, two categories of phosphinic acids, a reduced amide isostere, and an .alpha.,.alpha.-difluoroketone. The resulting **peptide analogues** were linear competitive inhibitors of purified recombinant HIV-1 protease with inhibition constants ranging from 18 nM to 40 .mu.M depending on the type of inhibitor. A truncated inhibitor, an **analogue** of a hexapeptide, retained full inhibitory potency. The most potent inhibitors, containing the hydroxyethylene isostere, effectively blocked the proteolytic processing of a recombinant form of Pr55(gag) by HIV-1 protease in a cell-free assay.

L13 ANSWER 32 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 21
ACCESSION NUMBER: 88209084 EMBASE
DOCUMENT NUMBER: 1988209084
TITLE: Adenallene and cytallene: Acyclic nucleoside analogues that inhibit replication and cytopathic effect of human immunodeficiency virus in vitro.
AUTHOR: Hayashi S.; Phadtare S.; Zemlicka J.; Matsukura M.; Mitsuya H.; Broder S.
CORPORATE SOURCE: The Clinical Oncology Program, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1988) 85/16 (6127-6131).
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 029 Clinical Biochemistry
047 Virology
037 Drug Literature Index
030 Pharmacology
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Although several antiretroviral compounds are already known, almost no acyclic nucleoside derivatives lacking an oxacyclopentane have been reported to exert significant inhibition against human immunodeficiency virus type 1 (HIV-1) in vitro. We found two unsaturated acyclic nucleoside derivatives, adenallene [9-(4'-hydroxy-1',2'-butadienyl)adenine] and cytallene [1-(4'-hydroxy-1',2'-butadienyl)cytosine], that protect various CD4+ T-cell lines from the infectivity and cytopathic effect of HIV-1. These compounds inhibit the expression of HIV-1 **gag**-encoded **protein** and suppress viral DNA synthesis at concentrations that do not affect functions of normal T cells in vitro. They also inhibit the in vitro infectivity of another human retrovirus, HIV-2. Further in vitro analyses of the anti-HIV-1 activity revealed that the presence of two cumulated double bonds between the 1' and 2' carbons and between the 2' and 3' carbons confers antiretroviral activity in certain pyrimidine or purine derivatives containing a four-carbon chain. We have also found that the 4'-hydroxyl group is critical for the in vitro anti-HIV activity of adenallene. Our observations may provide structure-activity relationships for acyclic nucleoside **analogues** and may be of value in developing a new class of experimental drugs for the therapy of HIV-related diseases.

L13 ANSWER 33 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 88067901 EMBASE
DOCUMENT NUMBER: 1988067901
TITLE: N-myristoylation of p60(src). Identification of a myristoyl-CoA:glycylpeptide N-myristoyltransferase in rat tissues.
AUTHOR: Glover C.J.; Goddard C.; Felsted R.L.
CORPORATE SOURCE: Laboratory of Biological Chemistry, Division of Cancer Treatment, Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD 20892, United States
SOURCE: Biochemical Journal, (1988) 250/2 (485-491).
ISSN: 0264-6021 CODEN: BIJOAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A 16-residue synthetic **peptide** corresponding to the N-terminal sequence of p60(src) was used as the acyl acceptor in an assay for myristoyl-CoA:glycylpeptide N-myristoyltransferase in rat tissues. An additional C-terminal tyrosine amide was added to this **peptide** to facilitate radioiodination and enhance detectability. Reverse-phase h.p.l.c. enabled the simultaneous detection and quantification of the **peptide** substrate and its N-myristoylated product. N-Myristoyltransferase activity was highest in the brain with decreasing activities in lung, small intestine, kidney, heart, skeletal muscle and liver. Brain activity was distributed approximately equally between the 100 000 g pellet and supernatant fractions. The soluble enzyme exhibited a K(m)(app.) of 20 .mu.M for the src **peptide** and an optimum between pH 7.0 and 7.5. Maximum N-acylating activity was seen with myristoyl (C(14:0))-CoA with lower activities found with the C(10:0)-CoA and C(12:0)-Coa homologues. No activity was obtained with palmitoyl (C(18:0))-CoA but this derivative inhibited N-myristoyltransferase activity > 50% at equimolar concentrations with myristoyl-CoA. With a decapeptide corresponding to the N-terminal sequence of the cyclic AMP-dependent **protein** kinase catalytic subunit as the acyl acceptor, the brain enzyme displayed a K(m)(app.) of 117 .mu.M and was about 14-fold less catalytically effective than with the p60(src) acyl acceptor. Transferase activity was also seen with a 16-residue **peptide** corresponding to the N-terminal sequence of the HIV p17(**gag**) structural **protein**. Inhibition studies with shorter src **peptide analogues** indicated an enzyme specificity for the p60(src) acyl acceptor beyond 9 residues.

L13 ANSWER 34 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89042837 EMBASE
DOCUMENT NUMBER: 1989042837
TITLE: Molecular biology of HIV.
AUTHOR: Peterlin B.M.; Luciw P.A.
CORPORATE SOURCE: Howard Hughes Medical Institute, University of California, San Francisco, CA 94143, United States
SOURCE: AIDS, (1988) 2/SUPPL. 1 (S29-S40).
ISSN: 0269-9370 CODEN: AIDSET
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
047 Virology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Much has been learned about HIV in the past 5 years. Sequencing of the viral genes was followed by the expression and characterizations of their **protein** products in prokaryotic and eukaryotic systems. Now, great efforts are being made to crystallize HIV **proteins** and examine their structures. This will allow for design and synthesis of chemical **analogues** that might interfere with the actions of HIV enzymes and trans-activators, block viral morphogenesis and budding, or prevent interactions between virions and cellular membranes. HIV has been isolated in many countries, from many individuals and from the same individual over time, and from different tissues in patients with distinct symptoms. These viral isolates will elucidate interactions between host immunity and HIV, determinants of viral tropism, and subtleties in the regulation of HIV gene expression. Closer examination of tat and rev might solve fundamental conundrums in retrovirology dealing with differences in the rates of initiation of transcription between the LTRs of the provirus and with the regulation of processing and splicing of viral transcripts. Cell biology of signaling, receptor mediated endocytosis and cell fusion will benefit from studies of **nef**, and of the interactions between env products, CD4 and other host receptors. Some of the above processes will be found responsible for HIV-induced cytopathology and cell death. As a consequence of these investigations, we hope that a chink in the armour of HIV will be found leading to therapeutics that will block the virus and ameliorate the symptoms or cure AIDS.

L13 ANSWER 35 OF 41 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1987:418282 BIOSIS
DOCUMENT NUMBER: BA84:84944
TITLE: PHARMACOLOGICAL INHIBITION OF IN-VITRO INFECTIVITY OF HUMAN T LYMPHOTROPIC VIRUS TYPE I.
AUTHOR(S): MATSUSHITA S; MITSUYA H; REITZ M S; BRODER S
CORPORATE SOURCE: CLINICAL ONCOLOGY PROGRAM, BUILD. 10, ROOM 13N238, NATL.

CANCER INST., BETHESDA, MD. 20892.
SOURCE: J CLIN INVEST, (1987) 80 (2), 394-400.
CODEN: JCINAO. ISSN: 0021-9738.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Human T lymphocytic virus type I (HTLV-I) is an exogenous RNA tumor virus etiologically linked to adult T cell leukemia and related diseases. In this paper, we describe that two 2',3'-dideoxynucleoside **analogues**, erythro 3'-azido-2',3'-dideoxy-thymidine (also called azidothymidine) and 2',3'-dideoxycytidine can inhibit the infectivity of HTLV-I against helper/inducer T cells in vitro. Both 2',3'-dideoxynucleoside **analogues** inhibited the overgrowth of target T cells, which was a consequence of virally mediated transformation, when they were exposed to the virus and cultured with the compounds. A profound decrease in the expression of HTLV-I **gag-proteins** was also observed. Moreover, we observed that the amount of proviral DNA detected in cellular DNA from the target T cells was substantially reduced when the cells were protected by the compounds against the virus and that at certain concentrations of the compounds the synthesis of viral DNA was completely suppressed. These results may be of value in developing a new pharmacological strategy for preventing the replication and possibly blocking the transmission of HTLV-I and related retroviruses in human beings.

L13 ANSWER 36 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 22
ACCESSION NUMBER: 86104838 EMBASE
DOCUMENT NUMBER: 1986104838
TITLE: Comparative inhibitory effects of suramin and other selected compounds on the infectivity and replication of human T-cell lymphotropic virus (HTLV-III)/lymphadenopathy-associated virus (LAV).
AUTHOR: Balzarini J.; Mitsuya H.; De Clercq E.; Broder S.
CORPORATE SOURCE: Rega Institute for Medical Research, University of Leuven, B-3000 Leuven, Belgium
SOURCE: International Journal of Cancer, (1986) 37/3 (451-457).
CODEN: IJCNAW
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
016 Cancer
025 Hematology
047 Virology
030 Pharmacology
026 Immunology, Serology and Transplantation
LANGUAGE: English
AB Suramin and various other selected compounds were evaluated for their in vitro inhibitory effects on the infectivity and replication of human T-cell lymphotropic virus (HTLV/III)/lymphadenopathy-associated virus (LAV). As parameters for infectivity and replication, respectively, we followed the cytopathic effect of HTLV-III/LAV on ATH 8 cells, a T-cell clone with high susceptibility to HTLV-III/LAV, and the expression of HTLV-III/LAV p24 **gag protein** in H9 cells infected with HTLV-III/LAV. As the most effective inhibitors of HTLV-III/LAV the following substances emerged (in order of decreasing activity): Evans Blue .simeq. suramin > phosphonoformic acid > Direct Yellow 50. Several purine nucleoside **analogues** including vidarabine, tubercidin, neplanocin A, dihydroxypropyladenine, pyrazofurin and ribavirin were not inhibitory to HTLV-III/LAV. In our test systems, involving a high multiplicity of infection, HPA-23, previously reported to be effective against LAV reverse transcriptase, showed no inhibitory effect on HTLV-III/LAV infectivity for ATH 8 cells and proved only weakly inhibitory to HTLV-III/LAV replication in H9 cells. Thus, among the anionic dyes that are structurally related to suramin, compounds were found which were as active as suramin itself, if not more so.

L13 ANSWER 37 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 86196219 EMBASE
DOCUMENT NUMBER: 1986196219
TITLE: Antibodies to the ATP-binding site of the human epidermal growth factor (EGF) receptor as specific inhibitors of EGF-stimulated protein-tyrosine kinase activity.
AUTHOR: Gullick W.J.; Downward J.; Foulkes J.G.; Waterfield M.D.
CORPORATE SOURCE: Protein Chemistry Laboratory, Imperial Cancer Research Fund Laboratories, London WC2A 3PX, United Kingdom
SOURCE: European Journal of Biochemistry, (1986) 158/2 (245-253).
CODEN: EJBCAI
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
LANGUAGE: English
AB A region of the primary amino acid sequence of the epidermal growth factor receptor (EGF) **protein**-tyrosine kinase, which is involved in ATP binding, was identified using chemical modification and immunological techniques. EGF receptor was 14C-labelled with the ATP **analogue** 5'-p-fluorosulphonylbenzoyladenosine and from a tryptic digest a single radiolabelled **peptide** was isolated. The amino acid sequence was determined to be residues 716-724 and hence lysine residue 721 is located within the ATP-binding site. Antisera were elicited in rabbits to a synthetic **peptide** identical to residues 716-727 of the EGF receptor and the homologous seqnece in v-erb B transforming **protein** from avian erythroblastosis virus. The affinity-purified antibodies precipitatetd human ECF receptor from A431 cells and placenta, and the v-erb B **protein** from erythroblasts. The antibodies inhibited EGF-stimulated receptor **protein**-tyrosine kinase autophosphorylation and phosphorylation of an exogenous **peptide** substrate containing tyrosine. The antibodies did not immunoprecipitate the transforming **proteins** pp60(v-scr) or P120(gag-abl) or cAMP-dependent **protein** kinase, **proteins** which have homologous but not identical sequences surrounding the lysine residue within the ATP-binding site, nor did they react with the platelet-derived growth factor receptor. The antibodies had no effect on the kinase activity of purified v-abl **protein** in solution. The antibodies may therefore be a specific inhibitor of the tyrosine kinase of the EGF receptor.

L13 ANSWER 38 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 23
ACCESSION NUMBER: 86063760 EMBASE
DOCUMENT NUMBER: 1986063760
TITLE: 3'-Azido-3'-deoxythymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of

human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro.
AUTHOR: Mitsuya H.; Weinhold K.J.; Furman P.A.; et al.
CORPORATE SOURCE: The Clinical Oncology Program, National Cancer Institute, Bethesda, MD 20205, United States
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1985) 82/20 (7096-7100).
CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
047 Virology
049 Forensic Science Abstracts
026 Immunology, Serology and Transplantation
016 Cancer
LANGUAGE: English
AB The acquired immune deficiency syndrome (AIDS) is thought to result from infection of T cells by a pathogenic human retrovirus, human T-lymphotropic virus type III (HTLV-III) or lymphadenopathy-associated virus (LAV). In this report, we describe the antiviral effects of a thymidine analogue, 3'-azido-3'-deoxythymidine (BW A509U), which, as a triphosphate, inhibits the reverse transcriptase of HTLV-III/LAV. This agent blocks the expression of the p24 gag protein of HTLV-III/LAV in H9 cells following exposure to virus. The drug also inhibits the cytopathic effect of HTLV-III(B) (a virus derived from a pool of American patients) and HTLV-III/RF-II (an isolate obtained from a Haitian patient that differs by about 20% in the amino acid sequence of the envelope gene from several isolates of HTLV-III/LAV, including HTLV-III(B), analyzed so far). 3'-Azido-3'-deoxythymidine also completely blocks viral replication as assessed by reverse transcriptase production in normal human peripheral blood mononuclear cells exposed to HTLV-III(B). Finally, at concentrations of 3'-azido-3'-deoxythymidine that blocks the in vitro infectivity and cytopathic effect of HTLV-III(B), the in vitro immune functions of normal T cells remain basically intact.

L13 ANSWER 39 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 78313217 EMBASE
DOCUMENT NUMBER: 1978313217
TITLE: Cell-free synthesis of a precursor polyprotein containing both gag and pol gene products by Rauscher murine leukemia virus 35S RNA.
AUTHOR: Murphy Jr. E.C.; Kopchick J.J.; Watson K.F.; Arlinghaus R.B.
CORPORATE SOURCE: Dept. Biol., Univ. Texas Syst. Cancer Cent., M.D. Anderson Hosp. Tum. Inst., Houston, Tex 77030, United States
SOURCE: Cell, (1978) 13/2 (359-369).
CODEN: CELLB5
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
025 Hematology
047 Virology
022 Human Genetics
LANGUAGE: English
AB Translation of Rauscher murine leukemia virus 35S RNA in mRNA-dependent m-RNA-dependent protein-synthesizing system results in the synthesis of polypeptides with apparent molecular weights of 200,000, 75,000 and 65,000 daltons. Each of these polypeptides was immunoprecipitable with anti-p30 serum, while only the 200,000 dalton size class was specifically recognized by antiserum prepared against purified reverse transcriptase. Intracellular Pr200(gag-pol) has been shown to contain p30 tryptic peptide sequences (Arcement et al., 1976) and to share antigenic determinants with the gag proteins p30, p15, p12 and p10 and the reverse transcriptase (Jamjoom, Naso and Arlinghaus, 1977). These results and others (Jamjoom et al., 1977) led the authors to the conclusion that Pr200(gag-pol) is the initial translation product that leads to the formation of mature reverse transcriptase. In the present study, 9 of 11 methionine-containing tryptic peptides found in an anti-reverse transcriptase-precipitable 80,000 dalton molecular weight virion polypeptide (p80(pol)) were contained in Pr200(gag-pol). In addition, virion p80(pol) co-migrates in SDS-polyacrylamide gels with the major polypeptide found in partially purified preparations of active reverse transcriptase. The in vitro synthesized 200,000 dalton polypeptide was identical to intracellular Pr200(gag-pol) as determined by comparing ion-exchange profiles of methionine-labeled tryptic peptides. The frequency of synthesis of the in vitro synthesized Pr200(gag -pol) was 1/25 to 1/20 that of the combined synthesis of the 65,000 and 75,000 dalton gag precursors. A similar ratio of Pr200(gag-pol) to Pr65(gag) and Pr80(gag) has been observed in viral infected cells. Thus 35S viral genomic RNA is an mRNA for both gag and pol gene products. Experiments with the arginine analogue canavanine suggest that the usual termination signal occurs after the translation of Pr80(gag). The authors propose that the Pr200(gag-pol) results from an occasional read-through (5% frequency) of a single termination codon at the end of the gag gene.

L13 ANSWER 40 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 78361411 EMBASE
DOCUMENT NUMBER: 1978361411
TITLE: Cell-free synthesis of Rauscher murine leukemia virus 'gag' and 'gag-pol' precursor polyproteins from virion 35 S RNA in a mRNA dependent translation system derived from mouse tissue culture cells.
AUTHOR: Murphy Jr. E.C.; Arlinghaus R.B.
CORPORATE SOURCE: Dept. Biol., Univ. Texas Syst. Cancer Cent., M.D. Anderson Hosp. Tum. Inst., Houston, Tex. 77030, United States
SOURCE: Virology, (1978) 86/2 (329-343).
CODEN: VIRLAX
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
047 Virology
LANGUAGE: English
AB Using a mRNA-dependent cell-free protein synthesis system derived from mouse tissue culture cell extracts by treatment with micrococcal nuclease, we have examined the capacity of 35S genomic RNA from Rauscher leukemia virus (RLV) to code for the synthesis of viral proteins. Analysis of the polypeptide product by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) indicated that RLV 35S RNA directed the synthesis of RLV-specific polypeptides of 55,000, 65,000,

75,000, and 200,000 apparent molecular weights, identical in size to the known intracellular precursors of the RLV mature polypeptides. None of the individual mature virus **proteins** appeared to be synthesized. If canavanine, an arginine **analogue**, was substituted for arginine under conditions for cell-free **protein** synthesis, a RLV-specific polypeptide with a molecular weight of approximately 80,000 was synthesized at the expense of the 65,000 and 75,000 MW polypeptides. Monospecific antisera directed against p30, p15, p12, and p10 recognized the 65,000, 75,000, 80,000 and 200,000 MW polypeptides, indicating that each shared antigenic determinants with all of these 'gag' **proteins**. Using the appropriate authentic RLV precursor polypeptides as standards, comparative tryptic maps were performed with the [3H]tyrosine or [35S]methionine-labeled in vitro-synthesized 65,000 and 200,000 MW polypeptides. The 65,000 MW polypeptide was found to be identical to Pr65(**gag**), a 65,000 MW RLV **gag** **protein** precursor obtained from infected cells by immunoprecipitation and gel electrophoresis. The 200,000 MW in vitro-synthesized polypeptide was found to contain methionine-labeled tryptic **peptides** characteristic of the RLV reverse transcriptase ('pol') and p30.

L13 ANSWER 41 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 78103275 EMBASE
DOCUMENT NUMBER: 1978103275
TITLE: Evolutionary relationships between gag gene-coded proteins of murine and primate endogenous type C RNA viruses.
AUTHOR: Barbacid M.; Stephenson J.R.; Aaronson S.A.
CORPORATE SOURCE: Lab. RNA Tum. Viruses, Nat. Cancer Inst., Bethesda, Md. 20014, United States
SOURCE: Cell, (1977) 10/4 (641-648).
CODEN: CELLB5
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 047 Virology
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
AB Several low molecular weight **proteins** of endogenous type C viruses of the RD114/baboon group are compared with the **gag** gene translational products of endogenous type C viruses of murine origin. The p10 **proteins** of each virus group are shown to be immunologically and biochemically related, while the p12 **proteins** of RD114/baboon viruses are demonstrated to share antigenic determinants with murine viral p15. Moreover, highly type-specific phosphoproteins, p15 of RD114/baboon viruses and p12 of murine viruses, are shown to possess very similar biochemical properties. These findings, along with previous studies indicating immunologic cross-reactivity between their major internal antigens, p30, demonstrate that each of the **gag** gene-coded **proteins** of murine type C viruses has an **analogue** in viruses of the RD114/baboon group. The immunologic and biochemical relatedness of their **gag** gene translational products supports the concept of a common progenitor in the evolution of these endogenous viruses.

=> dis his

(FILE 'HOME' ENTERED AT 12:18:33 ON 09 JUL 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:18:45 ON 09 JUL 2002
L1 20 S (NEF (1N) (84-92)) OR (GAG (1N) 77-85)
L2 5 DUP REM L1 (15 DUPLICATES REMOVED)
L3 207502 S ANALOGUE
L4 0 S L2 AND L3
L5 0 S L1 AND L3
L6 4675 S L3 AND HIV
L7 46831 S L3 (P) (PEPTIDE? OR PROTEIN?)
L8 184 S L7 (P) AIDS
L9 801 S L7 (P) (HIV OR NEF OR AIDS)
L10 847 S L7 (P) (HIV OR NEF OR AIDS OR GAG)
L11 110 S L7 (P) (NEF OR GAG)
L12 64 S L11 AND PD<19980507
L13 41 DUP REM L12 (23 DUPLICATES REMOVED)

=> s l7 (P) (HIV or AIDS)
L14 800 L7 (P) (HIV OR AIDS)

=> s l14 not nucleo?
L15 575 L14 NOT NUCLEO?

=> s l15 and PD<19980507
'19980507' NOT A VALID FIELD CODE
3 FILES SEARCHED...
L16 262 L15 AND PD<19980507

=> s l16 not l13
L17 244 L16 NOT L13

=> dup rem l17
PROCESSING COMPLETED FOR L17
L18 155 DUP REM L17 (89 DUPLICATES REMOVED)

=> s l18 and (NEF or GAG)
L19 15 L18 AND (NEF OR GAG)

=> dis l19 1-15 ibib abs

L19 ANSWER 1 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:258358 BIOSIS
DOCUMENT NUMBER: PREV199800258358
TITLE: Serological detection of attenuated HIV-1 variants with **nef** gene deletions.
AUTHOR(S): Greenway, Alison L.; Mills, John; Rhodes, David; Deacon, Nicholas J.; McPhee, Dale A. (1)
CORPORATE SOURCE: (1) ACBU, Natl. Cent. HIV Virol. Res., Macfarlane Burnet Cent. Med. Res., P.O. Box 254, Fairfield, VIC 3078 Australia
SOURCE: AIDS (London), (April 16, 1998) Vol. 12, No. 6, pp. 555-561.
ISSN: 0269-9370.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Objective: To investigate whether members of a transfusion-linked cohort (the Sydney Bloodbank Cohort) infected with a **nef**-deleted strain of HIV-1 could be differentiated from individuals infected with wild-type strains of HIV-1 by characterizing the **Nef** antibody response of cohort members. Design: Retrospective and prospective analysis of the **nef** gene sequence and the antibody response to **Nef peptides** in HIV-infected subjects. Methods: Plasma was obtained from all individuals of the Sydney cohort, and from a variety of HIV-1-infected and uninfected controls. Antibodies recognizing full-length recombinant HIV-1NL43 **Nef protein** and synthetic **peptide analogues** were assessed by enzyme-linked immunosorbent assay. Results: All 34 individuals infected with wild-type HIV-1 had antibodies reacting with full-length **Nef protein** as well as with a series of synthetic **peptides** (6-23-mers) spanning most of the **Nef protein** of HIV-1NL43. Although the HIV-1 quasispecies infecting the Sydney cohort had a consensus deletion of the **nef** gene corresponding to amino-acids 165-206, HIV-1 strains from individual members of the cohort had additional deletions comprising up to 80% of the **nef** gene. Members of the cohort had antibodies to **peptides** homologous to all regions of the **Nef protein** tested, except for a single **peptide** (amino-acids 162-177) that lies within the consensus **nef** deletion for the cohort quasispecies. Conclusion: These data show that **nef**-deleted strains of HIV-1 can be detected serologically. In the Sydney cohort, detection of antibodies to all regions of **Nef** tested, except that corresponding to amino-acids 162-177, suggests that observed deletions outside this domain occurred after this virus had infected these subjects and stimulated an immune response. A **Nef peptide** serological assay may be useful for identifying further examples of individuals infected with **nef**-deleted, attenuated HIV-1 quasispecies and for assessing the evolution of those variants in vivo.

L19 ANSWER 2 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:489083 BIOSIS
DOCUMENT NUMBER: PREV199799788286
TITLE: Transfer of the HIV-1 cyclophilin-binding site to simian immunodeficiency virus from Macaca mulatta can confer both cyclosporin sensitivity and cyclosporin dependence.
AUTHOR(S): Bukovsky, Anatoly A.; Weimann, Andreas; Accola, Molly A.; Gottlinger, Heinrich G.
CORPORATE SOURCE: Div. Human Retrovirol., Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA 02115 USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1997) Vol. 94, No. 20, pp. 10943-10948.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB HIV-1 specifically incorporates the peptidyl prolyl isomerase cyclophilin A (CyPA), the cytosolic receptor for the immunosuppressant cyclosporin A (CsA). HIV-1 replication is inhibited by CsA as well as by nonimmunosuppressive CsA **analogues** that bind to CyPA and interfere with its virion association. In contrast, the related simian immunodeficiency virus SIV-mac, which does not interact with CyPA, is resistant to these compounds. The incorporation of CyPA into HIV -1 virions is mediated by a specific interaction between the active site of the enzyme and the capsid (CA) domain of the HIV-1 **Gag** polyprotein. We report here that the transfer of HIV -1 CA residues 86-93, which form part of an exposed loop, to the corresponding position in SIV-mac resulted in the efficient incorporation of CyPA and conferred an HIV-1-like sensitivity to a nonimmunosuppressive cyclosporin. HIV-1 CA residues 86-90 were also sufficient to transfer the ability to efficiently incorporate CyPA, provided that the length of the CyPA-binding loop was preserved. However, the resulting SIV-mac mutant required the presence of cyclosporin for efficient virus replication. The results indicate that the presence or absence of a type II tight turn adjacent to the primary CyPA-binding site determines whether CyPA incorporation enhances or inhibits viral replication. By demonstrating that CyPA-binding-site residues can induce cyclosporin sensitivity in a heterologous context, this study provides direct in vivo evidence that the exposed loop between helices IV and V of HIV-1 CA not merely constitutes a docking site for CyPA but is a functional target of this cellular **protein**.

L19 ANSWER 3 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:251687 BIOSIS
DOCUMENT NUMBER: PREV199799550890
TITLE: The non-immunosuppressive cyclosporin A analogue SDZ NIM 811 inhibits cyclophilin A incorporation into virions and virus replication in human immunodeficiency virus type 1-infected primary and growth-arrested T cells.
AUTHOR(S): Mlynar, Edith (1); Bevec, Dorian; Billich, Andreas; Rosenwirth, Brigitte; Steinkasserer, Alexander (1)
CORPORATE SOURCE: (1) Sandoz Res. Inst., Brunnerstr. 59, A-1235 Vienna Austria
SOURCE: Journal of General Virology, (1997) Vol. 78, No. 4, pp. 825-835.
ISSN: 0022-1317.
DOCUMENT TYPE: Article
LANGUAGE: English
AB SDZ NIM 811 is a cyclosporin A (CsA) **analogue** that is completely devoid of immunosuppressive capacity but exhibits potent and selective antihuman immunodeficiency virus type 1 (HIV-1) activity. Binding to cyclophilin A, the intracellular receptor for cyclosporins, is a prerequisite for HIV-1 inhibition by cyclosporins. Cyclophilin A was demonstrated to bind to HIV-1 p24-**gag** and this cyclophilin-**Gag** interaction leads to the incorporation of cyclophilin A into HIV-1 virions. SDZ NIM 811 inhibits this **protein** interaction, and this is likely to be the molecular basis for its antiviral activity. Here, we show that in activated primary T cells SDZ NIM 811 interferes with two stages of the virus replication cycle: (i) translocation of pre-integration complexes into the nucleus and (ii) production of infectious virus particles. SDZ NIM 811 not only inhibits translocation of HIV-1 pre-integration complexes in primary T cells, but also in a growth-arrested T cell line. In vivo, most T lymphocytes are quiescent, but serve nevertheless as a major and inducible HIV-1 reservoir in infected individuals. Significant amounts of cyclophilin A were found to be associated with virus particles propagated in primary T cells. SDZ NIM 811 caused a strong reduction in the amount of incorporated cyclophilin A, thereby reducing infectivity.

Thus, cyclophilin A seems to be necessary for HIV-1 replication in primary T cells.

L19 ANSWER 4 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:43866 BIOSIS
DOCUMENT NUMBER: PREV199598058166
TITLE: Functional association of cyclophilin A with HIV-1 virions.
AUTHOR(S): Thali, Markus (1); Bukovsky, Anatoly; Kondo, Eisaku; Rosenwirth, Brigitte; Walsh, Christopher T.; Sodroski, Joseph; Gottlinger, Heinrich G.
CORPORATE SOURCE: (1) Inst. Microbiol., University Lausanne, CH-1066 Epalinges Switzerland
SOURCE: Nature (London), (1994) Vol. 372, No. 6504, pp. 363-365. ISSN: 0028-0836.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Cyclophilins are a family of **proteins** that bind the immunosuppressant cyclosporin A, possess peptidyl-prolyl cis-trans isomerase activity, and assist in the folding of **proteins**. Human cyclophilins A and B are host cell **proteins** that bind specifically to the HIV-1 **Gag** polyprotein p55-**gag** in vitro. Here we report that viral particles formed by p55-**gag**, in contrast to particles formed by the **Gag** polyproteins of other retroviruses, contain significant amounts of cyclophilin A. Sequences in the capsid domain of p55-gag are both required and sufficient for the virion-associated of cyclophilin A. The association of cyclophilin A with HIV-1 virions was inhibited in a dose-dependent manner by cyclosporin A as well as by SDZ NIM811 ((Melle-4)cyclosporin), a non-immunosuppressive **analogue** of cyclosporin A. Drug induced reductions in virion- associated cyclophilin A levels were accompanied by reductions in virion infectivity, indicating that the association is functionally relevant. Moreover, SDZ NIM811 inhibited the replication of HIV-1 but was inactive against SIV-MAC, a primate immunodeficiency virus closely related to HIV-1, which does not incorporate cyclophilin A.

L19 ANSWER 5 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:415321 BIOSIS
DOCUMENT NUMBER: PREV199396081046
TITLE: A survey of synthetic HIV-1 peptides with natural and chimeric sequences for differential reactivity with Zimbabwean, Tanzanian and Swedish HIV-1-positive sera.
AUTHOR(S): Blomberg, Jonas (1); Lawoko, Alex; Pipkorn, Ruediger; Moyo, Sylvester; Malmvall, Bo Erik; Shao, John; Dash, Rabinarayan; Tswana, Sam
CORPORATE SOURCE: (1) Section Virol., Dep. Med. Microbiol., Univ. Lund, Solvegatan 23d, S-223 62 Lund Sweden
SOURCE: AIDS (Philadelphia), (1993) Vol. 7, No. 6, pp. 759-767. ISSN: 0269-9370.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Objective: To determine whether the known sequence differences between African and non-African HIV-1 strains are reflected in the serological response. Design and methods: We investigated the antibody reactivity of 34 Swedish, 30 Tanzanian and 42 Zimbabwean HIV -1-positive sera to 67 synthetic **peptides** with sequences from North American and African HIV-1 isolates, mostly derived from regions of **gag** and env known to be antigenic. Not all sera were tested against all **peptides**. Results: Differences in frequency of reactivity were noted with **peptides** covering the entire third variable domain (V3), which is a primary neutralization determinant, and the carboxyl terminus of gp120, in two regions of gp41, and the carboxyl terminus of p24. In env Tanzanian sera reacted preferentially with a V3 **peptide** from the strain JY1 (Zaire). Gradual substitutions in the central motif in V3 of ELI from GLGQ to GPGR, typical of many non-African strains, led to a gradual increase in reactivity of many Swedish sera, but did not affect Tanzanian and Zimbabwean sera, suggesting that the major epitopes recognized by these African sera are outside GPGR. V3 **peptides** from the MN and Z3 strains reacted with most sera, but missed 30% of those of Tanzanian origin. In the carboxy terminus of gp120 both sets of African sera reacted preferentially with **peptides** from strains JY1 and MAL. Swedish sera reacted strongest with **analogues** from strains Z321 and HXB2. In gp41, Swedish sera showed a weak preference for reactivity with HXB2-derived **peptides** in the immunodominant region (amino acids 590-620), and further towards the carboxyl terminus (amino acids 620-665). Conclusion: The differences in serological reactivity were as great between Zimbabwe and Tanzania as between the two African sets and the Swedish. The geographical differences in the pattern of reactivity with **HIV peptides** probably depend on both host and viral variation and may be developed into a seroepidemiological tool, useful for optimization of future HIV vaccines.

L19 ANSWER 6 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:138235 BIOSIS
DOCUMENT NUMBER: PREV199395071035
TITLE: Inhibition of HIV by an anti-HIV protease synthetic peptide blocks an early step of viral replication.
AUTHOR(S): Venaud, S.; Yahi, N.; Fehrentz, J. L.; Guettari, N.; Nisato, D.; Hirsch, I.; Chermann, J. C. (1)
CORPORATE SOURCE: (1) Unite Recherches INSERM Retrovirus Maladies Associees, Campus Luminy, BP 33, 13273 Marseille Cedex 9 France
SOURCE: Research in Virology, (1992) Vol. 143, No. 5, pp. 311-319. ISSN: 0923-2516.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English; French
AB The processing of the human immunodeficiency virus (HIV) **gag** and **gag**-pol precursor **proteins** by the virus-encoded protease is an essential step in maturation of infectious virus particles. Like most retroviral proteases, the HIV protease belongs to the aspartyl-protease family and can be inhibited by specific inhibitors. Twenty-four synthetic **peptides** known to be inhibitors of human renin were tested for inhibition of HIV replication in tissue cultures. One of them, a synthetic **peptide analogue**, SR 41476, which has been shown to be a specific inhibitor of purified recombinant HIV1 protease in vitro, totally blocked infection with different isolates including the HIV1 LAV prototype, the highly cytopathic Zairian isolate HIV1 NDK, and HIV2 ROD, both in primary blood lymphocytes (PBL) and in the lymphoid cell lines MT4 and CEM, for at least 3 weeks. It also significantly reduced virus replication in chronically infected CEM cells, without any effect on cell proliferation. Radioimmunoprecipitation assay revealed that the inhibitor blocked

processing of polyprotein precursors p55 gag and p40 gag into a mature form of gag proteins, p25 and p18. Synthetic peptide analogue SR 41476, when added before infection, efficiently inhibited formation of HIV DNA provirus and successfully suppressed synthesis of HIV-specific proteins. These results imply that the HIV protease inhibitor not only inhibited virus maturation in the late phase of the HIV replication cycle, but also interfered in the early phase, before the provirus was formed. This mechanism of antiviral activity provides new possibilities and strategies for AIDS chemotherapy.

L19 ANSWER 7 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:73668 BIOSIS
DOCUMENT NUMBER: PREV199395038168
TITLE: Mechanism of inhibition of the retroviral protease by a Rous sarcoma virus peptide substrate representing the cleavage site between the gag p2 and p10 proteins.
AUTHOR(S): Cameron, Craig E.; Grinde, Bjorn; Jentoft, Joyce; Leis, Jonathan (1); Weber, Irene T.; Copeland, Terry D.; Wlodawer, Alexander
CORPORATE SOURCE: (1) Dep. Biochem., Case Western Reserve Univ. Sch. Med., 2119 Abington Rd., Cleveland, Ohio 44106-4935
SOURCE: Journal of Biological Chemistry, (1992) Vol. 267, No. 33, pp. 23735-23741.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The activity of the avian myeloblastosis virus (AMV) or the human immunodeficiency virus type 1 (HIV-1) protease on peptide substrates which represent cleavage sites found in the gag and gag-pol polyproteins of Rous sarcoma virus (RSV) and HIV-1 has been analyzed. Each protease efficiently processed cleavage site substrates found in their cognate polyprotein precursors. Additionally, in some instances heterologous activity was detected. The catalytic efficiency of the RSV protease on cognate substrates varied by as much as 30-fold. The least efficiently processed substrate, p2-p10, represents the cleavage site between the RSV p2 and p10 proteins. This peptide was inhibitory to the AMV as well as the HIV-1 and HIV-2 protease cleavage of other substrate peptides with K-i values in the 5-20 mu-M range. Molecular modeling of the RSV protease with the p2-p10 peptide docked in the substrate binding pocket and analysis of a series of single-amino acid-substituted p2-p10 peptide analogues suggested that this peptide is inhibitory because of the potential of a serine residue in the P1' position to interact with one of the catalytic aspartic acid residues. To open the binding pocket and allow rotational freedom for the serine in P1', there is a further requirement for either a glycine or a polar residue in P2' and/or a large amino acid residue in P3'. The amino aid residues in P1-P4 provide interactions for tight binding of the peptide in the substrate binding pocket.

L19 ANSWER 8 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:48802 BIOSIS
DOCUMENT NUMBER: PREV199395025104
TITLE: Synthesis of stereochemically defined phosphonamidate-containing peptides: Inhibitors for the HIV-1 proteinase.
AUTHOR(S): Camp, Nicholas P.; Hawkins, Paul C. D. (1); Hitchcock, Peter B.; Gani, David (1)
CORPORATE SOURCE: (1) Chem. Dep., Purdie Building, University, St. Andrews, Fife KY16 9ST UK
SOURCE: Bioorganic & Medicinal Chemistry Letters, (1992) Vol. 2, No. 9, pp. 1047-1052.
ISSN: 0960-894X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Phosphonamidate-containing peptidic substrate analogues of the HIV-1 gag-pol proteinase-reverse transcriptase junction)-Phe-PSI(PO-2-N)-(S)-Pro- and -Phe-PSI(P(OMe)O-N)-(S)-Pro-(, mimicks for the transition states for proteolysis, have been synthesised. The absolute stereochemistry at C-1 of the phosphonophenylalanine residue was determined by X-ray crystallography. Boc-(S)-Asn-Phe-PSI(PO-2-N)-(S)-Pro-(S)-Pro-(S)-Ile-NH-i-Bu and Boc-(S)-Asn-(R)-Phe-PSI(P(OMe)O-N)-(S)-Pro-(S)-Ile-NH-i-Bu inhibit the HIV-1 proteinase.

L19 ANSWER 9 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1991:479825 BIOSIS
DOCUMENT NUMBER: BA92:113585
TITLE: HIV-1 PROTEINASE IS REQUIRED FOR SYNTHESIS OF PRO-VIRAL DNA.
AUTHOR(S): BABOONIAN C; DALGLEISH A; BOUNTIFF L; GROSS J; OROSZLAN S; RICKETT G; SMITH-BURCHNELL C; TROKE P; MERSON J
CORPORATE SOURCE: PFIZER CENT. RES., SANDWICH, KENT, CT13 9NJ, ENGL.
SOURCE: BIOCHEM BIOPHYS RES COMMUN, (1991) 179 (1), 17-24.
CODEN: BBRCA9. ISSN: 0006-291X.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB HIV-1 proteinase activity is thought to occur primarily post-integration by cleaving the viral gag and Gag-Pol polyproteins. Its role in the pre-integration stages of viral replication, however, has not been studied in detail. Here we report that a synthetic peptide analogue, UK-88,947, which is a specific inhibitor of purified HIV-1 proteinase, inhibits the processing of the viral polyproteins in cultures of HIV-1 infected cells and prevents the formation of mature, infectious virions. Analysis of DNA from HIV-1 infected cells treated with UK-88,947 showed that viral DNA synthesis was inhibited when the compound was added to cultures one hour before infection. Similar results were obtained when AZT was used. Neither HIV-1 reverse transcriptase or the replication of FIV are inhibited by UK-88,947.

L19 ANSWER 10 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1991:343477 BIOSIS
DOCUMENT NUMBER: BA92:42852
TITLE: ANTIBODIES TO GP41 AND NEF IN OTHERWISE HIV-NEGATIVE HOMOSEXUAL MAN WITH KAPOSI'S SARCOMA.
AUTHOR(S): BOWDEN F J; MCPHEE D A; DEACON N J; CUMMING S A; DOHERTY R R; SONZA S; LUCAS C R; CROWE S M
CORPORATE SOURCE: MACFARLEN BURNET CENTRE MED. RES., YARRA BEND ROAD, FAIRFIELD, VICTORIA 3078, AUST.
SOURCE: LANCET (N AM ED), (1991) 337 (8753), 1313-1314.
CODEN: LANAAI.
FILE SEGMENT: BA; OLD

LANGUAGE: English
AB A homosexual man with histologically confirmed Kaposi's sarcoma remained seronegative for HIV-1, HIV-2, and HTLV-1 on conventional tests over a 4-year period. HIV cultures were also negative on thirteen separate occasions. However, serum antibodies to synthetic **peptide analogues** of the gp41 and **nef** regions of HIV-1 were consistently detected on an enzyme immunoassay. Tests with the polymerase chain reaction with primers directed to the gag and env regions were negative. The antigens to which the antibodies were produced might have come from a defective HIV mutant, another retrovirus, or a hitherto unknown "agent of Kaposi's sarcoma" with similar antigenic epitopes.

L19 ANSWER 11 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1991:71484 BIOSIS
DOCUMENT NUMBER: BA91:40144
TITLE: AN HIV-1 AND HIV-2 CROSS-REACTIVE CYTOTOXIC T-CELL EPITOPE.
AUTHOR(S): NIXON D F; HUET S; ROTHBARD J; KIENY M-P; DELCHAMBRE M; THIRIART C; RIZZA C R; GOTCH F M; MCMICHAEL A J
CORPORATE SOURCE: MOLECULAR IMMUNOL. GROUP, INST. MOLECULAR MED., JOHN RADCLIFFE HOSP., HEADINGTON, OXFORD OX3 9DU, UK.
SOURCE: AIDS (PHILA), (1990) 4 (9), 841-846.
CODEN: AIDSET. ISSN: 0269-9370.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The HLA-B27-restricted HIV gag cytotoxic T-lymphocyte (CTL) epitope, 265-279, is highly conserved amongst HIV-1 isolates, only one, HIV-1ELI, having a single amino acid substitution. Over the same region HIV-2 differs by five amino acids. As a broadly cross-protective **AIDS** vaccine should protect against infection from all isolates of HIV-1 and HIV -2, we tested CTL specific for the HIV-1 265-279 epitope with **peptide analogues** from HIV-1ELI, HIV -2 and two simian immunodeficiency virus (SIV) isolates, and with recombinant vaccinia viruses expressing the respective **gag** genes, to determine whether there was any cross-reactivity for this CTL epitope. CTL from the HIV-1-infected donor could recognize the HIV-1ELI **peptide**, the **HIV-2 peptide** and recombinant vaccinia virus-infected target and one of the two SIV **peptide**-treated targets. Epitopes that exhibit such cross-reactivity may be valuable in vaccine design.

L19 ANSWER 12 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:140327 BIOSIS
DOCUMENT NUMBER: BR38:61777
TITLE: INHIBITION OF HIV-1 PROTEASE IN INFECTED T-LYMPHOCYTES BY SYNTHETIC **PEPTIDE ANALOGUES**.
AUTHOR(S): MEEK T D; LAMBERT D M; DREYER G B; CARR T J; TOMASZEK T A JR; MOORE M L; STRICKLER J E; DEBOUCK C; HYLAND L J; ET AL
CORPORATE SOURCE: DEP. MED. CHEM., SMITH KLINE AND FRENCH LAB., 709 SWEDELAND RD., KING PRUSSIA, PA. 19406, USA.
SOURCE: Nature (London), (1990) 343 (6253), 90-92.
CODEN: NATUAS. ISSN: 0028-0836.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L19 ANSWER 13 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:116285 BIOSIS
DOCUMENT NUMBER: BA89:65776
TITLE: SUBSTRATE ANALOGUE INHIBITION AND ACTIVE SITE TITRATION OF PURIFIED RECOMBINANT HIV-1 PROTEASE.
AUTHOR(S): TOMASSELLI A G; OLSEN M K; HUI J O; STAPLES D J; SAWYER T K; HEINRIKSON R L; TOMICH C-S C
CORPORATE SOURCE: BIOPOLYMER CHEM. RES. UNIT, UPJOHN CO., KALAMAZOO, MICH. 49001.
SOURCE: BIOCHEMISTRY, (1990) 29 (1), 264-269.
CODEN: BICHAW. ISSN: 0006-2960.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The aspartyl protease of human immunodeficiency virus 1 (HIV-1) has been expressed in Escherichia coli at high levels, resulting in the formation of inclusion bodies which contain denatured insoluble aggregates of the protease. After solubilization of these inclusion bodies in guanidinium chloride, the protease was purified to apparent homogeneity by a single-step reverse-phase HPLC procedure. The purified, but inactive, **protein** was denatured in 8 M urea and refolded to produce the active protease. Enzyme activity was demonstrated against the substrate H-Val-Ser-Gln-Asn-Tyr-Pro-Ile-Val-OH, modeled after the cleavage region between residues 128 and 135 in the **HIV gag** polyprotein. With this substrate, a Vmax of 1.3 .+-. 0.2 .mu.mol/(min .cntdot. mg) and KM of 2.0 .+-. 0.3 mM were determined at pH 5.5. Pepstatin (Iva-Val-Val-Sta-Ala-Sta-OH) and substrate **analogues** with the Tyr-Pro residues substituted by Sta, by Phe .PSI.[CH2N]Pro, and by Leu.PSI.[CH(OH)CH2]Val inhibited the protease with KI values of 360 nM, 3690 nM, 3520 nM, and < 10 nM, respectively. All were competitive inhibitors, and the tightest binding compound provided an active site titrant for the quantitative determination of enzymatically active HIV-1 protease.

L19 ANSWER 14 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:86711 BIOSIS
DOCUMENT NUMBER: BA89:46062
TITLE: INHIBITION OF HUMAN IMMUNODEFICIENCY VIRUS 1 PROTEASE IN-VITRO RATIONAL DESIGN OF SUBSTRATE ANALOGUE INHIBITORS.
AUTHOR(S): DREYER G B; METCALF B W; TOMASZEK T A JR; CARR T J; CHANDLER A C III; HYLAND L; FAKHOURY S A; MAGAARD V W; MOORE M L; ET AL
CORPORATE SOURCE: DEP. PEPTIDE CHEM., SMITH KLINE AND FRENCH LAB., P.O. BOX 1539, KING OF PRUSSIA, PA. 19406-0939.
SOURCE: PROC NATL ACAD SCI U S A, (1989) 86 (24), 9752-9756.
CODEN: PNASA6. ISSN: 0027-8424.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Inhibitors of the protease from human immunodeficiency virus 1 (HIV-1) were designed, synthesized, and kinetically characterized. **Analogues** of a heptapeptide substrate of HIV-1 protease with sequence similar to the p17-p24 cleavage site in the natural substrate, Pr55gag, were synthesized in which the scissile dipeptide bond was replaced with bonds from six categories of stable mimics of an aspartic proteolysis transition state or intermediate. These mimics included an **analogue** of statine, hydroxyethylene isosteres, two categories of phosphinic acids, a reduced amide isostere, and an

.alpha.,.alpha.-difluoroketone. The resulting peptide analogues were linear competitive inhibitors of purified recombinant HIV-1 protease with inhibition constants ranging from 18 nM to 40 .mu.M depending on the type of inhibitor. A truncated inhibitor, an analogue of a hexapeptide, retained full inhibitory potency. The most potent inhibitors, containing the hydroxyethylene isostere, effectively blocked the proteolytic processing of a recombinant form of Pr55gag by HIV-1 protease in a cell-free assay.

L19 ANSWER 15 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1986:120637 BIOSIS
DOCUMENT NUMBER: BA81:31053
TITLE: 3' AZIDO-3'-DEOXYTHYMIDINE BW-A-509U AN ANTIVIRAL AGENT THAT INHIBITS THE INFECTIVITY AND CYTOPATHIC EFFECT OF HUMAN T LYMPHOTROPIC VIRUS TYPE III-LYMPHADENOPATHY-ASSOCIATED VIRUS IN-VITRO.
AUTHOR(S): MITSUYA H; WEINHOLD K J; FURMAN P A; ST CLAIR M H; LEHRMAN S N; GALLO R C; BOLOGNESI D; BARRY D W; BRODER S
CORPORATE SOURCE: CLINICAL ONCOLOGY PROGRAM, NATIONAL CANCER INST., BETHESDA, MD 20205.
SOURCE: PROC NATL ACAD SCI U S A, (1985) 82 (20), 7096-7100. CODEN: PNASA6. ISSN: 0027-8424.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The acquired immune deficiency syndrome (AIDS) is thought to result from infection of T cells by a pathogenic human retrovirus, human T-lymphotropic virus type III (HTLV-III) or lymphadenopathy-associated virus (LAV). In this report, we describe the antiviral effects of a thymidine analogue, 3'-azido-3'-deoxythymidine (BW A509U), which, as a triphosphate, inhibits the reverse transcriptase of HTLV-III/LAV. This agent blocks the expression of the p24 gag protein of HTLV-III/LAV in H9 cells following exposure to virus. The drug also inhibits the cytopathic effect of HTLV-IIIB (a virus derived from a pool of American patients) and HTLV-III/RF-II (an isolate obtained from a Haitian patient that differs by about 20% in the amino acid sequence of the envelope gene from several isolates of HTLV-III/LAV, including HTLV-IIIB, analyzed so far). 3'-Azido-3'-deoxythymidine also completely blocks viral replication as assessed by reverse transcriptase production in normal human peripheral blood mononuclear cells exposed to HTLV-IIIB. Finally, at concentrations of 3'-azido-3'-deoxythymidine that block the in vitro infectivity and cytopathic effect of HTLV-IIIB, the in vitro immune functions of normal T cells remain basically intact.

=> s guillet J?/au or guichard G?/au or ostankovitch M?/au or Connan F?/au or Quesnel A?au or Chaoppin J?/au or Briand J?/au or muller S?/au
'?' TRUNCATION SYMBOL NOT VALID WITHIN 'A?AU'
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The truncation symbol ? may be used only at the end of a search term. To specify a variable character within a word use '!', e.g., 'wom!n' to search for both 'woman' and 'women'. Enter "HELP TRUNCATION" at an arrow prompt (=>) for more information.

=> s guillet J?/au or guichard G?/au or ostankovitch M?/au or Connan F?/au or Quesnel A?/au or Chaoppin J?/au or Briand J?/au or muller S?/au
L20 8085 GUILLET J?/AU OR GUICHARD G?/AU OR OSTANKOVITCH M?/AU OR CONNAN F?/AU OR QUESNEL A?/AU OR CHAOPPIN J?/AU OR BRIAND J?/AU OR MULLER S?/AU

=> s l20 and peptide?
L21 1211 L20 AND PEPTIDE?

=> s l21 and (GAG OR ENV)
L22 58 L21 AND (GAG OR ENV)

=> s l21 and (GAG or NEF)
L23 79 L21 AND (GAG OR NEF)

=> dup rem l23
PROCESSING COMPLETED FOR L23
L24 26 DUP REM L23 (53 DUPLICATES REMOVED)

=> s l24 and analogue?
L25 0 L24 AND ANALOGUE?

=> dis l24 1-26 ibib abs

L24 ANSWER 1 OF 26 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 20012539996 MEDLINE
DOCUMENT NUMBER: 21240681 PubMed ID: 11342637
TITLE: Characteristics of HIV-1 Nef regions containing multiple CD8+ T cell epitopes: wealth of HLA-binding motifs and sensitivity to proteasome degradation.
AUTHOR: Choppin J; Cohen W; Bianco A; Briand J P; Connan F; Dalod M; Guillet J G
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies infectieuses et tumorales, Institut National de la Sante et de la Recherche Medicale, Unite 445, Institut Cochin de Genetique Moleculaire, Universite Rene Descartes, Paris, France.. choppin@cochin.inserm.fr
SOURCE: JOURNAL OF IMMUNOLOGY, (2001 May 15) 166 (10) 6164-9. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809
AB First and foremost among the many factors that influence epitope presentation are the degradation of Ag, which results in peptide liberation, and the presence of HLA class I molecules able to present the peptides to T lymphocytes. To define the regions of HIV-1 Nef that can provide multiple T cell epitopes, we analyzed the Nef sequence and determined that there are 73 peptides containing 81 HLA-binding motifs. We tested the binding of these peptides to six common HLA molecules (HLA-A2, -A3, -A24, -B7, -B8, and -B35), and we showed that most of them were efficient binders (54% of motifs), especially peptides associating with HLA-A3, -B7/35, and -B8 molecules. Nef peptides most frequently recognized by T cells of HIV-1-infected individuals were 90-97, 135-143,

71-81, 77-85, 90-100, 73-82, and 128-137. The frequency of T cell recognition was not directly related to the strength of peptide -HLA binding. The generation of Nef epitopes is crucial; therefore, we investigated the digestion by the 20S proteasome of a large peptide, Nef(66-100). This fragment was efficiently cleaved, and NH(2)-terminally extended precursors of epitope 71-81 were recognized by T cells of an HIV-1-infected individual. These results suggest that a high frequency of T cell recognition may depend on proteasome cleavage.

L24 ANSWER 2 OF 26 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001554913 MEDLINE
DOCUMENT NUMBER: 21487849 PubMed ID: 11602047
TITLE: Downregulation of major histocompatibility class I on human dendritic cells by HIV Nef impairs antigen presentation to HIV-specific CD8+ T lymphocytes.
AUTHOR: Andrieu M; Chassin D; Desoutter J F; Bouchaert I; Baillet M; Hanau D; Guillet J G; Hosmalin A
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, 27 rue du Fbg St-Jacques, 75014 Paris, France.
SOURCE: AIDS RESEARCH AND HUMAN RETROVIRUSES, (2001 Sep 20) 17 (14) 1365-70.
Journal code: 8709376. ISSN: 0889-2229.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011017
Last Updated on STN: 20020222
Entered Medline: 20011207

AB The HIV early regulatory Nef protein downregulates surface expression of major histocompatibility class I (MHC I) molecules on various immortalized cell lines and on T lymphocytes. MHC I-restricted presentation induces CD8+ T cell responses, which have a major role in limiting HIV infection. Induction of primary immune responses requires dendritic cells, which are major candidates as the first cells that can internalize the virus and present it to T cells in mucosal contamination. To test the effect of Nef on MHC I-restricted antigen presentation by dendritic cells, we used recombinant vaccinia viruses. Flow cytometric analysis of double labeling for a vaccinia protein and MHC I showed that HIV-1 Lai Nef indeed downregulated MHC I surface expression on dendritic cells. MHC I-restricted presentation to a Nef-specific CD8+ cell clone from an infected patient was decreased in an interferon gamma ELISpot assay. Presentation of a reverse transcriptase epitopic peptide on sorted Nef-infected cells was decreased in a peptide concentration-dependent way, confirming the role of MHC I downregulation in the impairment of the CD8+ cell-specific response. Therefore, Nef downregulates MHC I surface expression on human dendritic cells, impairing presentation to HIV-specific CD8+ cells. This action of Nef probably induces a deleterious delay in the early CD8+ responses during the first days of infection and at the onset of new viral mutants.

L24 ANSWER 3 OF 26 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001401183 MEDLINE
DOCUMENT NUMBER: 21318631 PubMed ID: 11426068
TITLE: Lipopeptides induce cell-mediated anti-HIV immune responses in seronegative volunteers.
AUTHOR: Pialoux G; Gahery-Segard H; Sermet S; Poncelet H; Fournier S; Gerard L; Tartar A; Gras-Masse H; Levy J P; Guillet J G
CORPORATE SOURCE: Hopital Rothschild, Paris, France. (ANRS VAC 04 Study Team). gilles.pialoux@rth.ap-hop-paris.fr
SOURCE: AIDS, (2001 Jul 6) 15 (10) 1239-49.
Journal code: 8710219. ISSN: 0269-9370.
PUB. COUNTRY: England: United Kingdom
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB OBJECTIVE: Test the efficacy of a mixture of six NEF (N1, N2, N3), GAG (G1, G2) and ENV (E) lipopeptides in the induction of B- and T-cell anti-HIV responses. DESIGN: A randomized phase I open-label dose-finding trial. Twenty-eight healthy seronegative volunteers received the lipopeptides, with or without the adjuvant QS21. METHODS: Anti-HIV-peptide antibodies were detected by enzyme-linked immunosorbent assay and Western blotting. Induction of cellulary responses was assessed by proliferative test and (51)Cr-release assay. RESULTS: Local and systemic adverse reactions were always mild or moderate. After three injections an antibody response was detected in 25 out of 28 volunteers (89%). T cells from 19 (79%) of the 24 volunteers proliferated in response to at least one peptide. The majority of the volunteers had induced a multispecific proliferative response; that is, cells from volunteers proliferated to two (five of 19), three (five of 19), four (three of 19) or five peptides (one of 19). Cytotoxic responses by anti-HIV CD8+ lymphocytes could be tested in 24 volunteers, 13 (54%) of whom had clear and reproducible responses, with strong activity in the remaining 12 (> 20% of specific lysis), and polyepitopic responses were detected in at least seven of the 13 responders. Cytotoxic responses were found against the whole NEF protein (clade B LAI) in three of four tested volunteers and cross-reactions with the proteins of clade B (MN) and clade A (Bangui) HIV-1 strains, and also HIV-2 ROD, were detected in one of two tested volunteers. CONCLUSIONS: Lipopeptides are promising immunogens for an AIDS vaccine.

L24 ANSWER 4 OF 26 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001133497 MEDLINE
DOCUMENT NUMBER: 21066732 PubMed ID: 11145897
TITLE: DNA vaccination of macaques with several different Nef sequences induces multispecific T cell responses.
AUTHOR: Couillin I; Letourneur F; Lefebvre P; Guillet J G ; Martinon F
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, Paris, France.

SOURCE: VIROLOGY, (2001 Jan 5) 279 (1) 136-45.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010301

AB CD8(+) T lymphocytes play a key role in controlling viremia during primary human immunodeficiency virus-1 and in maintaining disease-free infection. It has recently been shown that DNA immunization of rhesus monkeys can elicit strong, long-lived antigen-specific cytotoxic T lymphocyte (CTL) responses. In previous work, it was shown that macaque CTL responses to lipopeptide vaccination were directed against a limited number of epitopes. In the present study, we used the DNA immunization approach to enlarge T cell responses to several epitopes and to multiple isolates. We immunized macaques with a mixture of six plasmids reflecting the variability of **Nef** epitopic regions in the simian immunodeficiency virus (SIV) mac251 primary isolate. The **Nef** genes from viruses included in the SIVmac251 primary isolate were sequenced and the six selected sequences were individually subcloned into the pCI vector, under cytomegalovirus enhancer/promoter control, and injected into macaques. We show that DNA immunization with **Nef** sequences induced interferon-gamma (IFN-gamma) secreting cell responses directed against several regions of **Nef**. Reacting T cell lines were expanded in vitro and multispecific CTL responses mapping the 96-138 **Nef** region were analyzed. Several **peptides** recognized by CTL were identified and studies using **peptides** reflecting the variability of **Nef** indicated that all of the **Nef** variants were recognized in the 96-138 region. Moreover, CTL responses were directed against an immunodominant epitope located in a functional region within the **Nef** protein that is essential for viral replication. This work shows that our approach of DNA immunization with several sequences induced multispecific T cell responses recognizing variants included in the SIVmac251 primary isolate.

L24 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:881190 CAPLUS
DOCUMENT NUMBER: 134:41099
TITLE: Polyepitopic **peptides** derived from the **Nef** protein of HIV-1 for vaccine use
INVENTOR(S): Choppin, Jeannine; Bourgault, Villada Isabelle; **Guillet, Jean-Gerard**; **Connan, Francine**; Perries, Estelle
PATENT ASSIGNEE(S): Biovector Therapeutics, Fr.; Institut National De La Sante Et De La Recherche Medicale-Inserm; Bourgault Villada, Isabelle
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000075181	A1	20001214	WO 2000-FR1514	20000531
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2794370	A1	20001208	FR 1999-7012	19990603
EP 1181314	A1	20020227	EP 2000-936995	20000531
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: FR 1999-7012 A 19990603
WO 2000-FR1514 W 20000531

AB The invention relates to the use of polyepitopic fragments of a detd. protein for the prodn. of medicaments designed to prevent or treat pathologies in which said protein is recognized by the cellular immune system and said polyepitopic fragments are chosen from the HIV **Nef** protein. The invention also relates to polyepitopic proteinic fragments of the HIV **Nef** protein, a method for the prodn. and use thereof, esp. in the field of vaccination.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 6 OF 26 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000111287 MEDLINE
DOCUMENT NUMBER: 20111287 PubMed ID: 10644339
TITLE: Multiepitopic B- and T-cell responses induced in humans by a human immunodeficiency virus type 1 lipopeptide vaccine.
AUTHOR: Gah ery-S egard H; Pialoux G; Charmeteau B; Sermet S; Poncelet H; Raux M; Tartar A; L evy J P; Gras-Masse H; **Guillet J G**
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM Unit e 445, Institut Cochin de G en etique Mol eculaire, Universit e Ren ee Descartes, H opital Cochin, 75014 Paris, France.. gahery@icgm.cochin.inserm.fr
SOURCE: JOURNAL OF VIROLOGY, (2000 Feb) 74 (4) 1694-703.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000302

AB We have attempted to develop an anti-human immunodeficiency virus (HIV) lipopeptide vaccine with several HIV-specific long **peptides** modified by C-terminal addition of a single palmitoyl chain. A mixture of six lipopeptides derived from regulatory or structural HIV-1 proteins (

Nef, Gag, and Env) was prepared. A phase I study was conducted to evaluate immunogenicity and tolerance in lipopeptide vaccination of HIV-1-seronegative volunteers given three injections of either 100, 250, or 500 microg of each lipopeptide, with or without immunoadjuvant (QS21). This report analyzes in detail B- and T-cell responses induced by vaccination. The lipopeptide vaccine elicited strong and multiepitopic B- and T-cell responses. Vaccinated subjects produced specific immunoglobulin G antibodies that recognized the Nef and Gag proteins. After the third injection, helper CD4(+)-T-cell responses as well as specific cytotoxic CD8(+) T cells were also obtained. These CD8(+) T cells were able to recognize naturally processed viral proteins. Finally, specific gamma interferon-secreting CD8(+) T cells were also detected ex vivo.

L24 ANSWER 7 OF 26 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2001102747 MEDLINE
DOCUMENT NUMBER: 20569537 PubMed ID: 11118377
TITLE: Temporal loss of Nef-epitope CTL recognition following macaque lipopeptide immunization and SIV challenge.
AUTHOR: Mortara L; Letourneur F; Villefroy P; Beyer C; Gras-Masse H; Guillet J G; Bourgault-Villada I
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, Institut Cochin de Genetique Moleculaire (ICGM), INSERM U445, 27 rue du Faubourg Saint-Jacques, Paris, 75014, France.
SOURCE: VIROLOGY, (2000 Dec 20) 278 (2) 551-61.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010126

AB To address the subtle interactions between antiviral cytotoxic T-cell (CTL) immune responses and the evolution of viral quasispecies variants in vivo, we performed a longitudinal study in a simian immunodeficiency virus (SIV)-infected rhesus macaque that had a long experimental SIV infection before developing simian AIDS. Before being infected with SIV, this animal was immunized with a mixture of seven lipopeptides derived from SIV Nef and Gag proteins and showed a bispecific antiviral CTL response directed toward Nef 169-178 and 211-225 peptides. After SIV infection, CTL activity against the Nef 169-178 epitope was no longer detectable, as assessed from peripheral blood mononuclear cells stimulated by autologous SIV. CTL activity against the 211-225 epitope was lost after 3 months, and an additional CTL response to the amino acids 112-119 Nef epitope emerged. Analysis of the Nef proviral sequence revealed the presence of immune escape variants first in the 211-225 epitope and much later in the 112-119 epitope. In contrast, epitope 169-178 showed only two mutations among all viral sequencing performed. We conclude that in this macaque, bispecific CTL exerted a strong selective pressure and escape virus mutants finally emerged. We identified CTL recognizing a conserved Nef epitope 112-119 (SYKLAIDM), essential for viral replication, which could be associated with a prolonged AIDS-free period. These results stress the importance of the induction of broader multispecific CTLs directed against highly conserved and functional T-cell epitopes by vaccination, with the aim of keeping HIV infection in check.

L24 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:659413 CAPLUS
DOCUMENT NUMBER: 131:270954
TITLE: Lipopeptides inducing cytotoxic T lymphocytes cytotoxicity and bearing at least one auxiliary T epitope with improved solubility for use in vaccines
INVENTOR(S): Le Gal, Frederique Anne; Guillet, Jean Gerard ; Gahery-Segard, Hanne; Gras-Masse, Helene; Melnyk, Oleg; Tartar, Andre
PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale INSERM, Fr.; Centre National de la Recherche Scientifique; Institut Pasteur de Lille
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9951630	A1	19991014	WO 1999-FR792	19990406
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2776926	A1	19991008	FR 1998-4323	19980407
CA 2328294	AA	19991014	CA 1999-2328294	19990406
AU 9930413	A1	19991025	AU 1999-30413	19990406
EP 1068226	A1	20010117	EP 1999-911884	19990406
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002512941	T2	20020508	JP 2000-542351	19990406

PRIORITY APPLN. INFO.: FR 1998-4323 A 19980407
WO 1999-FR792 W 19990406

AB Lipopeptides carrying cytotoxic T lymphocyte epitopes and auxiliary T cell epitopes that have good soly. and that can be used in vaccines are described. The peptides have the epitopes and the lipid-binding domains sepd. by hydrophilic peptides (1-10, preferably 2-4 residues) rich in amino acids carrying charges at neutral pH, particularly arginine. The peptides may be conventional linear peptides or the hydrophilic peptides may be used to crosslink peptides via side chains. Such peptides may be used in vaccines inducing an immune response against HIV and BHV, papillomavirus, melanoma p53, or malaria. Palmitoylated peptides carrying an auxiliary epitope of tetanus toxin and a cytotoxic

T-lymphocyte epitope of the MART-1 receptor recognized by HLA A2.1 were synthesized. One **peptide** using an alanine spacer was practically insol. in water, while others with improved soly. had spacers contg. arginine and glycine were sol. The **peptides** stimulated secretion of interferon .gamma. from cytotoxic T lymphocytes responding to the MART-1 epitope and the monopalmitoylated **peptide** was more effective than the epitope alone or a dipalmitoylated **peptide**. Tests with T cells from HIV-infected patients indicated that multiepitopic lipopeptides were recognized by individuals with expressing different class I HLA antigens.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 26 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999214387 MEDLINE
DOCUMENT NUMBER: 99214387 PubMed ID: 10196344
TITLE: Type 1 CD4(+) T-cell help is required for induction of antipeptide multispecific cytotoxic T lymphocytes by a lipopeptidic vaccine in rhesus macaques.
AUTHOR: Mortara L; Gras-Masse H; Rommens C; Venet A; **Guillet J G**; Bourgault-Villada I
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445-Universite Rene Descartes, Hopital Cochin, 75014 Paris,. France.mortara@cochin.inser.fr
SOURCE: JOURNAL OF VIROLOGY, (1999 May) 73 (5) 4447-51.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 19990601
Entered Medline: 19990519

AB We have optimized the induction of antiviral cytotoxic T lymphocytes (CTL) in rhesus macaques by a lipopeptide vaccine containing seven **peptides** from simian immunodeficiency virus (SIV) **Nef** and **Gag** proteins and a strong T-helper **peptide** from tetanus toxoid (TT) that is promiscuous in humans (**peptide** TT 830-846). Two of the eight immunized macaques showed T-helper (Th) cell proliferation and a specific synthesis of gamma interferon in response to TT 830-846 **peptide**. They also showed multispecific cytotoxic activity against three to five of the immunizing SIV **peptides**. These results show the importance of a strong specific type 1 Th response for inducing a multispecific CTL response in vivo, which is essential for the development of an anti-human immunodeficiency virus vaccine.

L24 ANSWER 10 OF 26 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2000029790 MEDLINE
DOCUMENT NUMBER: 20029790 PubMed ID: 10562305
TITLE: Weak anti-HIV CD8(+) T-cell effector activity in HIV primary infection.
AUTHOR: Dalod M; Dupuis M; Deschemin J C; Goujard C; Deveau C; Meyer L; Ngo N; Rouzioux C; **Guillet J G**; Delfraissy J F; Sinet M; Venet A
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, Unite Institut National de la Sante et de la Recherche Medicale (INSERM) 445, Institut Cochin de Genetique Moleculaire, Universite Rene Descartes, 75014 Paris, France.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1999 Nov) 104 (10) 1431-9.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991209

AB HIV-specific CD8(+) T cells play a major role in the control of virus during HIV primary infection (PI) but do not completely prevent viral replication. We used IFN-gamma enzyme-linked immunospot assay and intracellular staining to characterize the ex vivo CD8(+) T-cell responses to a large variety of HIV epitopic **peptides** in 24 subjects with early HIV PI. We observed HIV-specific responses in 71% of subjects. **Gag** and **Nef peptides** were more frequently recognized than Env and Pol **peptides**. The number of **peptides** recognized was low (median 2, range 0-6). In contrast, a much broader response was observed in 30 asymptomatic subjects with chronic infection: all were responders with a median of 5 **peptides** recognized (range 1-13). The frequency of HIV-specific CD8(+) T cells among PBMC for a given **peptide** was of the same order of magnitude in both groups. The proportion of HIV-specific CD8(+)CD28(-) terminally differentiated T cells was much lower in PI than at the chronic stage of infection. The weakness of the immune response during HIV PI could partially account for the failure to control HIV. These findings have potential importance for defining immunotherapeutic strategies and establishing the goals for effective vaccination.

L24 ANSWER 11 OF 26 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1999129881 MEDLINE
DOCUMENT NUMBER: 99129881 PubMed ID: 9933101
TITLE: Dendritic cells transfected with the **nef** genes of HIV-1 primary isolates specifically activate cytotoxic T lymphocytes from seropositive subjects.
AUTHOR: Chassin D; Andrieu M; Cohen W; Culmann-Penciolelli B; **Ostankovitch M**; Hanau D; **Guillet J G**
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, ICGM, Universite Rene Descartes, Paris, France.. chassin@icgm.cochin.inserm.fr
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Jan) 29 (1) 196-202.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990301
Last Updated on STN: 19990301
Entered Medline: 19990216

AB The HIV-1 **Nef** protein down-modulates surface expression of MHC class I proteins. Primary infected T lymphocytes thus escape lysis by cytotoxic T lymphocytes (CTL). In contrast, during HIV-1 infection there are strong CTL responses to several HIV proteins, and there is mounting evidence that CTL are critical for controlling the virus. The present study was carried out to assess **Nef** protein-cell interaction as it occurs in naturally infected antigen-presenting cells. To evaluate the presentation of **peptides** derived from viral antigen to CTL, we transfected **nef** genes obtained from peripheral blood mononuclear cells of HIV-1-seropositive subjects into dendritic cells isolated from monocytes of healthy donors. We demonstrate that expression and subsequent processing of **Nef** by transfected dendritic cells did not alter the presentation of an immunodominant epitope of **Nef** to CTL of HIV+ subjects. However, mutations in **nef** gene sequences from primary isolates may abolish this presentation by a mechanism that probably interferes with protein processing.

L24 ANSWER 12 OF 26 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998105786 MEDLINE
DOCUMENT NUMBER: 98105786 PubMed ID: 9445041
TITLE: Selection of virus variants and emergence of virus escape mutants after immunization with an epitope vaccine.
AUTHOR: Mortara L; Letourneur F; Gras-Masse H; Venet A; **Guillet J G**; Bourgault-Villada I
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, Paris, France.. mortara@icgm.cochin.inserm.fr
SOURCE: JOURNAL OF VIROLOGY, (1998 Feb) 72 (2) 1403-10. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980218

AB In this report, we assessed the evolution of the cytotoxic T-lymphocyte (CTL) response induced by an epitope vaccine. In two macaques immunized with a mixture of lipopeptides derived from simian immunodeficiency virus (SIV) **Nef** and **Gag** proteins, CTL responses were directed against the same, single epitope of the **Nef** protein (amino acids 128 to 137) presenting an alanine at position 136 (**Nef** 128-137/136A). However, after 5 months of SIV infection, peripheral blood mononuclear cells from both macaques lost their ability to be stimulated by autologous SIV-infected cells while still retaining their capacity to generate cytotoxic responses after specific **Nef** 128-137/136A **peptide** stimulation. The sequences of the pathogenic viral isolate used for the challenge showed a mixture of several variants. Within the **Nef** epitopic sequence from amino acids 128 to 137, 82% of viral variants expressed the epitopic **peptide Nef** 128-137/136A; the remaining variants presented a threonine at position 136 (**Nef** 128-137/136T). In contrast, sequence analysis of cloned proviral DNA obtained from both macaques 5 months after SIV challenge showed a different pattern of quasi-species variants; 100% of clones presented a threonine at position 136 (**Nef** 128-137/136T), suggesting the disappearance of viral variants with an alanine at this position under antiviral pressure exerted by **Nef** 128-137/136A-specific CTLs. In addition, 12 months after SIV challenge, six of eight clones from one macaque presented a glutamic acid at position 131 (**Nef** 128-137/131E+136T), which was not found in the infecting isolate. Furthermore, CTLs generated very early after SIV challenge were able to lyse cells sensitized with the **Nef** 128-137/136A epitope. In contrast, lysis was significantly less effective or even did not occur when either the selected **peptide Nef** 128-137/136T or the escape variant **peptide Nef** 128-137/131E+136T was used in a target cell sensitization assay. Dose analysis of **peptides** used to sensitize target cells as well as a major histocompatibility complex (MHC)-**peptide** stability assay suggested that the selected **peptide Nef** 128-137/136T has an altered capacity to bind to the MHC. These data suggest that CTL pressure leads to the selection of viral variants and to the emergence of escape mutants and supports the fact that immunization should elicit broad CTL responses.

L24 ANSWER 13 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:433011 CAPLUS
DOCUMENT NUMBER: 125:112540
TITLE: Among all human T-cell leukemia virus type 1 proteins, tax, polymerase, and envelope proteins are predicted as preferential targets for the HLA-A2-restricted cytotoxic T-cell response
AUTHOR(S): Pique, Claudine; **Connan, Francine**; Levilain, Jean-Pierre; Choppin, Jeannine; Dokhelar, Marie-Christine
CORPORATE SOURCE: URA 1156 CNRS and Service Immuno-Hematologie, Inst. Gustave Roussy, Paris, Fr.
SOURCE: J. Virol. (1996), 70(8), 4919-4926
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The human T-cell leukemia virus type 1 (HTLV-1) is a human retrovirus assocd. with two diseases for which no successful treatment is yet available; the development of a vaccine is therefore an important issue. Since HTLV-1 is a persistent virus, an efficient vaccine will probably require a cytotoxic T-lymphocyte (CTL) response in addn. to the prodn. of antibodies. To identify potential CTL epitopes, we have selected, within all of the HTLV-1 proteins, nonapeptides contg. anchor residues required for assocn. with HLA-A2 mols. (residues at positions 2 and 9), which is the most frequently occurring A allele in all human populations. A set of 111 **peptides** was synthesized and tested in vitro in two assembly assays using processing-defective T2 cells. Anchor motifs selected were those contg. two major anchor residues (L2/M2/K2-/V9/L9/I9) (one letter amino-acid code) and those including tolerated anchor residues (V2/A2/T2 and/or A9/M9/T9). The anal. of the binding capacity of the **peptides** confirms the high efficiency of the L2-V9 anchor motif and shows that a systematic research of potential binding **peptides** should exclude **peptides** contg. known detrimental residues rather than select only **peptides** with known favored residues. We show that 39 **peptides** representative of all the HTLV-1 proteins are able to bind to HLA-A2 mols. Strong binder **peptides** which are very likely good CTL epitopes were identified in three HTLV-1 proteins, Tax, envelope, and polymerase. Three of the strong binder

peptides correspond to previously described HLA-A2-restricted CTL epitopes in the Tax protein, and two others are localized in a domain of the viral envelope recognized by natural neutralizing antibodies. This latter result has important implications for the development of an anti-HTLV-1 vaccine.

L24 ANSWER 14 OF 26 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 95220421 MEDLINE
DOCUMENT NUMBER: 95220421 PubMed ID: 7705402
TITLE: HLA-dependent variations in human immunodeficiency virus Nef protein alter peptide/HLA binding.
AUTHOR: Couillin I; Connan F; Culmann-Penciolelli B; Gomard E; Guillet J G; Choppin J
CORPORATE SOURCE: Unite 152, Institut National de la Sante et de la Recherche Medicale, Institut Cochin de Genetique, Moleculaire, Paris, France.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Mar) 25 (3) 728-32. Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19970203
Entered Medline: 19950509

AB In human immunodeficiency virus (HIV) infection, sequence variations within defined cytotoxic T lymphocyte (CTL) epitopes may lead to escape from CTL recognition. In a previous report, we have shown that the variable central region of HIV Nef protein (amino acids 73-144) that contains potential CTL epitopes, can escape the CTL response. We suggested that this non recognition occurs through a variety of mechanisms. In particular, we provided evidence that HIV Nef sequences recovered from HLA-A11-expressing individuals have alterations in the major anchor residues essential for binding of the two Nef epitopes (amino acids 73-82 and 84-92) to the HLA-A11 molecule. Here, we investigate in more detail whether variations in autologous Nef sequences affect HLA binding, leading to CTL escape. Potential epitopes were sought by testing Nef peptides containing the HLA-A11-specific motif or related motifs. We confirmed that only the two previously described epitopes identified in cytolysis tests have optimal reactivity with the HLA-A11 molecule. We then sequenced several viral variants from donors that do not express the HLA-A11 molecule and compared the variability of these epitopes with those obtained from HLA-A11-expressing individuals. One substitution (Leu85) found in the sequences isolated from both populations increase the reactivity of the HLA-A11-restricted epitope 84-92, and might explain the difference in immunogenicity observed between the two HLA-A11-restricted epitopes from HLA-A11+ individuals. In addition, selective variations were only detected in virus isolated from HLA-A11-expressing individuals. Furthermore, examination of the association of variant peptides with the HLA-A11 molecule demonstrated that a single substitution within the minimal epitope could not always completely abrogate HLA binding, suggesting that multiple alterations within a particular epitope may accumulate during disease progression, allowing the virus to escape CTL recognition.

L24 ANSWER 15 OF 26 MEDLINE
ACCESSION NUMBER: 95074927 MEDLINE
DOCUMENT NUMBER: 95074927 PubMed ID: 7983767
TITLE: Identification of multirestricted immunodominant regions recognized by cytolytic T lymphocytes in the human immunodeficiency virus type 1 Nef protein.
AUTHOR: Culmann-Penciolelli B; Lamhamedi-Cherradi S; Couillin I; Guegan N; Levy J P; Guillet J G; Gomard E
CORPORATE SOURCE: Laboratoire d'Immunologie des Interactions Cellulaires et Molecularies Institut National de la Sante de la Recherche Medicale U152, Paris, France.
SOURCE: JOURNAL OF VIROLOGY, (1995 Jan) 69 (1) 618. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Errata; (PUBLISHED ERRATUM)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950116
Last Updated on STN: 19950116
Entered Medline: 19950105

L24 ANSWER 16 OF 26 MEDLINE
ACCESSION NUMBER: 94266816 MEDLINE
DOCUMENT NUMBER: 94266816 PubMed ID: 8206929
TITLE: Two pairs of oppositely charged amino acids from Jun and Fos confer heterodimerization to GCN4 leucine zipper.
AUTHOR: John M; Briand J P; Granger-Schnarr M; Schnarr M
CORPORATE SOURCE: Institut de Biologie Moleculaire et Cellulaire du CNRS, UPR 9002, Strasbourg, France.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Jun 10) 269 (23) 16247-53. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940721
Last Updated on STN: 19940721
Entered Medline: 19940713

AB The preferential assembly of Jun and Fos into heterodimers has been shown to be mainly driven by 16 amino acids (8 from each protein) situated in positions e and g of the leucine zipper coiled-coil structures of the two proteins (O'Shea, E. K., Rutkowski, R., and Kim, P. S. (1992) Cell 68, 699-708). Using a similar approach, we show that among these residues two pairs of oppositely charged amino acids account in fact for most of the additional free energy of heterodimerization in this system. These residues are 2 glutamic acid side chains in positions g1 and e2 of the Fos leucine zipper and 2 lysine residues in the equivalent positions of the Jun zipper. These amino acids were placed in the context of a GCN4 leucine zipper using peptide synthesis. These peptides contain unique cysteine residues enabling the formation of covalent dimers. The gain in heterodimer free energy has been determined both by cysteine-linked dimer formation under redox conditions and by thermal melting experiments of covalent dimers using circular dichroism

experiments. The two pairs of oppositely charged residues (Glu,Glu and Lys,Lys) in positions g1 and e2 contribute at least -1.9 kcal/mol of additional free energy, accounting for a 50-fold excess of the heterodimer with respect to one of the homodimers. Thermal denaturation studies as a function of pH and ionic strength suggest that electrostatic effects should indeed be a major driving force for heterodimerization. On the contrary, **peptides** harboring the 12 amino acids from Jun and Fos in the other e and g positions (i.e. in e1, g2, e3, g3, e4, and g4) show only a moderate tendency to form heterodimers.

L24 ANSWER 17 OF 26 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 95018646 MEDLINE
DOCUMENT NUMBER: 95018646 PubMed ID: 7523699
TITLE: Identification of multirestricted immunodominant regions recognized by cytolytic T lymphocytes in the human immunodeficiency virus type 1 **Nef** protein.
COMMENT: Erratum in: J Virol 1995 Jan;69(1):618
AUTHOR: Culmann-Penciolelli B; Lamhamedi-Cherradi S; Couillin I; Guegan N; Levy J P; **Guillet J G**; Gomard E
CORPORATE SOURCE: Laboratoire d'Immunologie des Interactions Cellulaires et Moleculaires, Institut National de la Sante et de la Recherche Medicale U152. Institut Cochin de Genetique Moleculaire, Paris, France.
SOURCE: JOURNAL OF VIROLOGY, (1994 Nov) 68 (11) 7336-43.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19970203
Entered Medline: 19941117

AB Peripheral blood mononuclear cells from a large number of human immunodeficiency virus (HIV)-seropositive donors were used to analyze the CD8+ T-cell response to each part of the **Nef** protein of HIV-1/LAI. This report identifies an immunodominant region (amino acids 73 to 144) in the **Nef** protein that was recognized by 97% of the **NEF** responder donors. This **peptide** sequence was dissected into four epitopic regions (amino acids 73 to 82, 83 to 97, 113 to 128, and 126 to 144), each of which was recognized under different HLA class I restrictions. Short overlapping **peptides** were used to sensitive the target cells for cytolysis and so to determine if these epitopic regions were multirestricted. Each region was found to contain several epitopes recognized with different HLA molecules. Thus, the central region of the **Nef** protein, a regulatory protein expressed early in HIV-infected cells, is rich in epitopic sequences which are found to be similar in many infected individuals and which can be recognized in association with at least ten HLA class I molecules. Their implications for the vaccination of humans with **peptide** sequences are discussed.

L24 ANSWER 18 OF 26 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 94179836 MEDLINE
DOCUMENT NUMBER: 94179836 PubMed ID: 8133061
TITLE: Simian immunodeficiency virus as a model for vaccination against HIV. Induction in rhesus macaques of **GAG**- or **NEF**-specific cytotoxic T lymphocytes by lipopeptides.
AUTHOR: Bourgault I; Chirat F; Tartar A; Levy J P; **Guillet J G**; Venet A
CORPORATE SOURCE: Cochin Institute of Molecular Genetics, Cochin Hospital, Paris, France.
SOURCE: JOURNAL OF IMMUNOLOGY, (1994 Mar 1) 152 (5) 2530-7.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940428
Last Updated on STN: 19970203
Entered Medline: 19940419

AB The protection against infection by HIV probably requires the induction of both neutralizing Abs and CTL responses. Vaccination by attenuated HIV is hardly acceptable and the use of viral genes inserted in recombinant living vectors needs further development, especially with respect to safety. The peptidic vaccination is a promising approach but free **peptides** are usually poorly immunogenic. Because potent immune responses have been obtained in mice with modified **peptides** such as lipopeptides, we have designed a study to assess the immunogenicity of lipopeptides in nonhuman primates. Seven lipopeptides were synthesized, derived from known immunogenic regions of the simian immunodeficiency virus (SIV) **NEF** and **GAG** proteins. Twelve rhesus macaques, randomly chosen and not selected on their MHC basis, were immunized subcutaneously with the seven lipopeptides in IFA. An MHC class I-restricted and CD(8+)-mediated CTL response has been observed in seven macaques directed against one or two of the synthetic immunizing **peptides** in each case. These CTLs were able to lyse autologous target cells infected with a recombinant vaccinia virus expressing the SIV **nef** or **gag** genes, suggesting that they recognized the naturally processed **peptides**. These activities are detectable in peripheral blood cells for at least 10 mo after the last immunization. Abs against the immunizing **peptides** have also been observed in all cases. This study demonstrates that lipopeptides can generate cytotoxic and humoral immune responses in a large number of unselected animals and this approach may thus be worth considering in the vaccination against HIV.

L24 ANSWER 19 OF 26 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 94342829 MEDLINE
DOCUMENT NUMBER: 94342829 PubMed ID: 7520468
TITLE: Impaired cytotoxic T lymphocyte recognition due to genetic variations in the main immunogenic region of the human immunodeficiency virus 1 **NEF** protein.
COMMENT: Comment in: J Exp Med. 1994 Sep 1;180(3):779-82
AUTHOR: Couillin I; Culmann-Penciolelli B; Gomard E; Choppin J; Levy J P; **Guillet J G**; Saragosti S
CORPORATE SOURCE: Institut National de la Sante el de la Recherche Medicale, Unit *363, Paris, France.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Sep 1) 180 (3) 1129-34.
Journal code: 2985109R. ISSN: 0022-1007.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19941005
Last Updated on STN: 19970203
Entered Medline: 19940922

AB Human immunodeficiency virus (HIV) induces strong responses from human histocompatibility leukocyte antigen (HLA) class I-restricted cytotoxic T lymphocytes (CTL). In a previous report we identified an immunodominant region (amino acids 73-144) in the **NEF** protein that was recognized by CD8+ class I-restricted CTL of most asymptomatic individuals. Analysis of the 73-144 region by **peptide** sensitization, experiments using overlapping **peptides** corresponding to the LAI isolate identified the **peptide** sequences located between residues 73 and 82 or 84 and 92 and the **peptide** sequence between residues 134 and 144 as cognate **peptides** for HLA-A11- and HLA-B18-restricted epitopes, respectively. This report describes the variable demonstrable reactivities of CTL obtained from HLA-A11 or HLA-B18 seropositive, asymptomatic patients who all had a response to the virus **NEF** protein, but who did not always recognize appropriate cognate **peptides**. The high mutation rate of HIV probably facilitates the selection of mutants that can avoid the cellular immune response. We therefore analyzed the variability of these epitopes restricted by HLA-A11 and HLA-B18. We sequenced several viral isolates from HLA-A11 and HLA-B18 donors who recognized certain HLA-**peptide** complexes and from those who did not. A CTL sensitization assay was used to show that some mutations led to a great reduction in CTL activity in vitro. This might be due to failure of the mutated epitope to bind major histocompatibility complex class I molecule. A simple assay was used to detect **peptides** that promoted the assembly of class I molecules. Some of these mutations at major anchor positions prevented HLA-A11/**peptide** binding, and consequently impaired recognition of the HLA-**peptide** complex by the T cell receptor.

L24 ANSWER 20 OF 26 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 94170859 MEDLINE
DOCUMENT NUMBER: 94170859 PubMed ID: 8125145
TITLE: A simple assay for detection of **peptides** promoting the assembly of HLA class I molecules.
AUTHOR: **Connan F**; Hlavac F; Hoebeke J; **Guillet J G**; Choppin J
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), INSERM U152, Paris, France.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 Mar) 24 (3) 777-80.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940420
Last Updated on STN: 19940420
Entered Medline: 19940412

AB Synthetic **peptides** derived from influenza virus and human immunodeficiency virus were tested for their ability to promote the assembly of HLA-A2 and HLA-B51 molecules in T2 cell lysates. Specific assembly was detected by an enzyme-linked immunosorbent assay. The most significant HLA-A2 assembly was obtained in the presence of **peptides** known to be targets for HLA-A2-restricted cytotoxic T lymphocytes (influenza matrix M.58-66 and HIV Pol 476-484). Three of a batch of **Nef peptides** corresponding to epitopic regions for cytotoxic T lymphocytes, caused significant assembly of HLA-A2 (**Nef** 83-91, 137-145 and 144-153), but only at high concentrations (100 microM). As these **peptides** bound relatively weakly, it is unlikely that they are good candidates for HLA-A2-restricted CTL epitopes. **Peptides** matrix M.60-68, **Nef** 186-194, and Plasmodium falciparum sh.77-85 produced the most significant assembly of HLA-B51. These **peptides** have a dominant hydrophobic anchor residue (V, L. I) at position 9 that could occupy pocket "F". Our results also suggest that another hydrophobic residue (V, L) at position 3 or 4 may anchor to hydrophobic pocket "D" of HLA-B51. Proline at position 2 greatly increases HLA-B51 anchoring.

L24 ANSWER 21 OF 26 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:445486 BIOSIS
DOCUMENT NUMBER: PREV199345081111
TITLE: SIV as a model for vaccination against HIV: Induction by lipopeptides in rhesus macaques of **GAG** or **NEF** specific cytotoxic T lymphocytes (CTL.
AUTHOR(S): Bourgault, I.; Chirat, F.; Tartar, A.; **Guillet, J. G.**; Levy, J. P.; Venet, A.
CORPORATE SOURCE: ICGM, INSERM U152, Hopital Cochin, 27 rue du Faubourg Saint Jacques, 75014 Paris France
SOURCE: IXTH INTERNATIONAL CONFERENCE ON AIDS AND THE IVTH STD WORLD CONGRESS.. (1993) pp. 253. IXth International Conference on AIDS in affiliation with the IVth STD World Congress.
Publisher: IXth International Conference on AIDS Berlin, Germany.
Meeting Info.: Meeting Berlin, Germany June 6-11, 1993
DOCUMENT TYPE: Conference
LANGUAGE: English

L24 ANSWER 22 OF 26 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:445267 BIOSIS
DOCUMENT NUMBER: PREV199345080892
TITLE: Detection of HLA-A2 and HLA-B5 **peptide** binding motifs in the HIV-1 **Nef** protein.
AUTHOR(S): **Connan, F.**; Hlavac, F.; **Guillet, J. G.**; Choppin, J.
CORPORATE SOURCE: ICGM, INSERM U152, Hopital Cochin, 27 rue du Fg St. Jacques, 75014 Paris France
SOURCE: IXTH INTERNATIONAL CONFERENCE ON AIDS AND THE IVTH STD WORLD CONGRESS.. (1993) pp. 216. IXth International Conference on AIDS in affiliation with the IVth STD World Congress.
Publisher: IXth International Conference on AIDS Berlin, Germany.
Meeting Info.: Meeting Berlin, Germany June 6-11, 1993
DOCUMENT TYPE: Conference

LANGUAGE: English

L24 ANSWER 23 OF 26 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 93039645 MEDLINE
DOCUMENT NUMBER: 93039645 PubMed ID: 1384546
TITLE: HLA class I binding regions of HIV-1 proteins.
AUTHOR: Choppin J; Guillet J G; Levy J P
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), INSERM U152, Paris, France.
SOURCE: CRITICAL REVIEWS IN IMMUNOLOGY, (1992) 12 (1-2) 1-16. Ref: 82
Journal code: 8914819. ISSN: 1040-8401.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19970203
Entered Medline: 19921210

AB To identify HIV **peptides** containing HLA class I binding regions, different studies have been performed. These include the detection of interactions between HIV **peptides** and purified HLA molecules in solid-phase assays, the measurement of HLA molecule assembly in the presence of **peptide** added to cell lysates, and the detection of inhibition of CTL-mediated cytolysis by competition between **peptides** on target cells. To date, the HIV epitopes recognized by anti-HIV CTL are from the Env, **Gag**, **Nef**, and Pol proteins and they are identified using synthetic **peptides** of 12 to 20 amino acids. The search for a correlation between known HIV CTL epitopes and the results of HLA/**peptide** interaction assays reveals that: (1) most of the **peptides** that are positive in the assembly assay contain a HLA-A2 **peptide** motif but the correlation between these positive **peptides** and the CTL epitopes is not obvious; (2) a high proportion of HIV epitopes are included in the **peptides** positive in solid-phase binding and in inhibition of cytolysis assays, although these tests do not allow us to predict HLA restriction; (3) the HLA-A2 **peptide** motif is not systematically included in HLA-A2-restricted CTL epitopes, this observation raising the possibility that other sequences are involved in HLA binding.

L24 ANSWER 24 OF 26 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 91302806 MEDLINE
DOCUMENT NUMBER: 91302806 PubMed ID: 1712812
TITLE: HLA-binding regions of HIV-1 proteins. II. A systematic study of viral proteins.
AUTHOR: Choppin J; Martinon F; **Connan F**; Pauchard M; Gomard E; Levy J P
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), INSERM U152, Paris, France.
SOURCE: JOURNAL OF IMMUNOLOGY, (1991 Jul 15) 147 (2) 575-83.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910908
Last Updated on STN: 19970203
Entered Medline: 19910820

AB To detect HLA-binding **peptides** in 10 HIV-1 proteins (Rev, Tat, Vif, Vpr, Vpu, **Gag** p18, **Gag** p24, **Gag** p15, Env gp120 and Env gp41), the **peptide** binding assay (PBA) has been performed using three HLA class I molecules. Correlations have been searched between the PBA results and the **peptide** competitor activity in a functional test using HLA-A2-restricted CTL and target cells. A correlation between the data found in the PBA and well-defined CTL epitopes could be attempted only for the three **Gag** proteins. For these proteins, our results are in agreement with the known existence of epitopes reacting with human CD8+ CTL, with some exceptions. Together with the results reported with a panel of **Nef peptides**, these experiments showed that at least 18/20 of the already reported CTL epitopes from HIV-1 **Gag**, **Nef**, and Env proteins could be detected by the PBA, most (17/18) corresponding to strong reactivities. Perhaps more important, the regions of HIV-1 **Gag** p24 or **Nef** proteins that contain multiple associated CTL epitopes, with different HLA restrictions, were clearly identified by the reactivities in the PBA of several overlapping **peptides** and the major practical interest of the PBA might be the detection of such polyepitopic regions. Prediction are proposed in this report for 10 proteins, including several proteins for which CTL epitopes remain presently unknown.

L24 ANSWER 25 OF 26 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 91302805 MEDLINE
DOCUMENT NUMBER: 91302805 PubMed ID: 1712811
TITLE: HLA-binding regions of HIV-1 proteins. I. Detection of seven HLA binding regions in the HIV-1 **Nef** protein.
AUTHOR: Choppin J; Martinon F; **Connan F**; Gomard E; Levy J P
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), Laboratoire d'Immunologie et Oncologie des Maladies, Retrovirales, INSERM U152, Paris, France.
SOURCE: JOURNAL OF IMMUNOLOGY, (1991 Jul 15) 147 (2) 569-74.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910908
Last Updated on STN: 19970203
Entered Medline: 19910820

AB The physical association of HLA class I or H-2 molecules with 36 HIV-1 **Nef** synthetic **peptides** was studied using a direct **peptide** binding assay (PBA) in solid phase. To assess the functional significance of the PBA results, the **Nef peptides** were also tested for their ability to inhibit the lytic activity of human or murine CTL. The PBA results showed that seven partly overlapping regions of the **Nef** protein contained MHC binding **peptides** (4-18, 46-67, 73-94, 100-128, 126-155, 182-198, and

192-206). Five of these seven regions included all the already described epitopes recognized by CD8+ human CTL. The two other regions, 4-18 and 46-67, are not yet described as antigenic for human CD8+ cells but they are located in the N-terminal part of Nef that was previously described as being stimulator for rat or chimpanzee CD4+ cells. Altogether, it can be concluded that 1) In virtually 100% of the cases, the PBA is capable to detect known antigenic peptides recognized by CTL. 2) The PBA and the functional inhibition assay provide similar results, supporting the functional significance of PBA results. 3) The PBA is easy to handle on a large scale, using multiple peptide and several MHC molecules, so that it can be used as a routine method for prevision of possibly epitopic sequences. 4) Systematic studies of peptides issued from the whole sequence of a given protein allow to map polyepitopic areas that are probably the most interesting parts of proteins for a vaccine purpose.

L24 ANSWER 26 OF 26 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:629080 CAPLUS
DOCUMENT NUMBER: 113:229080
TITLE: Analysis of physical interactions between peptides and HLA molecules and application to the detection of human immunodeficiency virus 1 antigenic peptides
AUTHOR(S): Choppin, Jeannine; Martinon, Frederic; Gomard, Elisabeth; Bahraoui, Elmostafa; Connan, Francine; Bouillot, Michel; Levy, Jean Paul
CORPORATE SOURCE: Hop. Cochin, Paris, 75014, Fr.
SOURCE: J. Exp. Med. (1990), 172(3), 889-99
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The phys. assocn. of 40 antigenic peptides and purified HLA class I and class II mols. was monitored using a direct peptide binding assay (PBA) in solid phase and an inhibition peptide binding assay (IPBA) in which the competing peptide was present in a sol. phase. The ability was also examd. of different peptides to inhibit the lytic activity of human antiviral cytolytic T cells towards cells incubated with the corresponding target peptide. Binding of a given human T cell-recognized peptide to several HLA class I and class II mols. occurred frequently. Nevertheless, preferential binding of peptides to their resp. restriction mols. was also obsd. Binding of HLA mols. to peptides recognized by murine T cells occurred less frequently. Eleven of 24 (46%) randomly selected HIV-1 peptides contained agretopic residues allowing their binding to HLA mols. The kinetics of HLA/peptide assocn. depended on the peptide tested and were faster than or similar to those reported for Ia mols. Dissocn. of these complexes was very low. Peptide/HLA mol. binding was dependent on length, no. of pos. charges, and presence of hydrophobic residues in the peptide. A correlation was demonstrated between a peptide inhibitory effect in the IPBA and its blocking effect in the cytolytic test. The restriction phenomenon obsd. in T cell responses was not strictly related to either an elective HLA/peptide assocn., or a high binding capacity of a peptide to HLA mols. Also, the PBA and IPBA are appropriate for the detection of agretopic residues within HIV-1 proteins.

=> dis his

(FILE 'HOME' ENTERED AT 12:18:33 ON 09 JUL 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:18:45 ON 09 JUL 2002
L1 20 S (NEF (1N) (84-92)) OR (GAG (1N) 77-85)
L2 5 DUP REM L1 (15 DUPLICATES REMOVED)
L3 207502 S ANALOGUE
L4 0 S L2 AND L3
L5 0 S L1 AND L3
L6 4675 S L3 AND HIV
L7 46831 S L3 (P) (PEPTIDE? OR PROTEIN?)
L8 184 S L7 (P) AIDS
L9 801 S L7 (P) (HIV OR NEF OR AIDS)
L10 847 S L7 (P) (HIV OR NEF OR AIDS OR GAG)
L11 110 S L7 (P) (NEF OR GAG)
L12 64 S L11 AND PD<19980507
L13 41 DUP REM L12 (23 DUPLICATES REMOVED)
L14 800 S L7 (P) (HIV OR AIDS)
L15 575 S L14 NOT NUCLEO?
L16 262 S L15 AND PD<19980507
L17 244 S L16 NOT L13
L18 155 DUP REM L17 (89 DUPLICATES REMOVED)
L19 15 S L18 AND (NEF OR GAG)
L20 8085 S GUILLET J?/AU OR GUICHARD G?/AU OR OSTANKOVITCH M?/AU OR CONN
L21 1211 S L20 AND PEPTIDE?
L22 58 S L21 AND (GAG OR ENV)
L23 79 S L21 AND (GAG OR NEF)
L24 26 DUP REM L23 (53 DUPLICATES REMOVED)
L25 0 S L24 AND ANALOGUE?

=> s l24 and analogu?
L26 0 L24 AND ANALOGU?

=> s l24 and analog?
L27 0 L24 AND ANALOG?

=> s l24 and variant?
L28 4 L24 AND VARIANT?

=> s l24 and variant?
L29 4 L24 AND VARIANT?

=> s l24 and derivativ?
L30 0 L24 AND DERIVATIV?

=> dis l29 1-4 ibib abs

L29 ANSWER 1 OF 4 MEDLINE
ACCESSION NUMBER: 2001133497 MEDLINE
DOCUMENT NUMBER: 21066732 PubMed ID: 11145897
TITLE: DNA vaccination of macaques with several different Nef sequences induces multispecific T cell responses.
AUTHOR: Couillin I; Letourneur F; Lefebvre P; Guillet J G

; Martinon F
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, Paris, France.
SOURCE: VIROLOGY, (2001 Jan 5) 279 (1) 136-45.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010301

AB CD8(+) T lymphocytes play a key role in controlling viremia during primary human immunodeficiency virus-1 and in maintaining disease-free infection. It has recently been shown that DNA immunization of rhesus monkeys can elicit strong, long-lived antigen-specific cytotoxic T lymphocyte (CTL) responses. In previous work, it was shown that macaque CTL responses to lipopeptide vaccination were directed against a limited number of epitopes. In the present study, we used the DNA immunization approach to enlarge T cell responses to several epitopes and to multiple isolates. We immunized macaques with a mixture of six plasmids reflecting the variability of **Nef** epitopic regions in the simian immunodeficiency virus (SIV) mac251 primary isolate. The **Nef** genes from viruses included in the SIVmac251 primary isolate were sequenced and the six selected sequences were individually subcloned into the pCI vector, under cytomegalovirus enhancer/promoter control, and injected into macaques. We show that DNA immunization with **Nef** sequences induced interferon-gamma (IFN-gamma) secreting cell responses directed against several regions of **Nef**. Reacting T cell lines were expanded in vitro and multispecific CTL responses mapping the 96-138 **Nef** region were analyzed. Several **peptides** recognized by CTL were identified and studies using **peptides** reflecting the variability of **Nef** indicated that all of the **Nef variants** were recognized in the 96-138 region. Moreover, CTL responses were directed against an immunodominant epitope located in a functional region within the **Nef** protein that is essential for viral replication. This work shows that our approach of DNA immunization with several sequences induced multispecific T cell responses recognizing **variants** included in the SIVmac251 primary isolate.

L29 ANSWER 2 OF 4 MEDLINE
ACCESSION NUMBER: 2001102747 MEDLINE
DOCUMENT NUMBER: 20569537 PubMed ID: 11118377
TITLE: Temporal loss of **Nef**-epitope CTL recognition following macaque lipopeptide immunization and SIV challenge.
AUTHOR: Mortara L; Letourneur F; Villefroy P; Beyer C; Gras-Masse H; **Guillet J G**; Bourgault-Villada I
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, Institut Cochin de Genetique Moleculaire (ICGM), INSERM U445, 27 rue du Faubourg Saint-Jacques, Paris, 75014, France.
SOURCE: VIROLOGY, (2000 Dec 20) 278 (2) 551-61.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010126

AB To address the subtle interactions between antiviral cytotoxic T-cell (CTL) immune responses and the evolution of viral quasispecies **variants** in vivo, we performed a longitudinal study in a simian immunodeficiency virus (SIV)-infected rhesus macaque that had a long experimental SIV infection before developing simian AIDS. Before being infected with SIV, this animal was immunized with a mixture of seven lipopeptides derived from SIV **Nef** and **Gag** proteins and showed a bispecific antiviral CTL response directed toward **Nef** 169-178 and 211-225 **peptides**. After SIV infection, CTL activity against the **Nef** 169-178 epitope was no longer detectable, as assessed from peripheral blood mononuclear cells stimulated by autologous SIV. CTL activity against the 211-225 epitope was lost after 3 months, and an additional CTL response to the amino acids 112-119 **Nef** epitope emerged. Analysis of the **Nef** proviral sequence revealed the presence of immune escape **variants** first in the 211-225 epitope and much later in the 112-119 epitope. In contrast, epitope 169-178 showed only two mutations among all viral sequencing performed. We conclude that in this macaque, bispecific CTL exerted a strong selective pressure and escape virus mutants finally emerged. We identified CTL recognizing a conserved **Nef** epitope 112-119 (SYKLAIDM), essential for viral replication, which could be associated with a prolonged AIDS-free period. These results stress the importance of the induction of broader multispecific CTLs directed against highly conserved and functional T-cell epitopes by vaccination, with the aim of keeping HIV infection in check.

L29 ANSWER 3 OF 4 MEDLINE
ACCESSION NUMBER: 1998105786 MEDLINE
DOCUMENT NUMBER: 98105786 PubMed ID: 9445041
TITLE: Selection of virus **variants** and emergence of virus escape mutants after immunization with an epitope vaccine.
AUTHOR: Mortara L; Letourneur F; Gras-Masse H; Venet A; **Guillet J G**; Bourgault-Villada I
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, Paris, France..
mortara@icgm.cochin.inserm.fr
SOURCE: JOURNAL OF VIROLOGY, (1998 Feb) 72 (2) 1403-10.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980218

AB In this report, we assessed the evolution of the cytotoxic T-lymphocyte

(CTL) response induced by an epitope vaccine. In two macaques immunized with a mixture of lipopeptides derived from simian immunodeficiency virus (SIV) **Nef** and Gag proteins, CTL responses were directed against the same, single epitope of the **Nef** protein (amino acids 128 to 137) presenting an alanine at position 136 (**Nef** 128-137/136A). However, after 5 months of SIV infection, peripheral blood mononuclear cells from both macaques lost their ability to be stimulated by autologous SIV-infected cells while still retaining their capacity to generate cytotoxic responses after specific **Nef** 128-137/136A **peptide** stimulation. The sequences of the pathogenic viral isolate used for the challenge showed a mixture of several **variants**. Within the **Nef** epitopic sequence from amino acids 128 to 137, 82% of viral **variants** expressed the epitopic **peptide Nef** 128-137/136A; the remaining **variants** presented a threonine at position 136 (**Nef** 128-137/136T). In contrast, sequence analysis of cloned proviral DNA obtained from both macaques 5 months after SIV challenge showed a different pattern of quasi-species **variants**; 100% of clones presented a threonine at position 136 (**Nef** 128-137/136T), suggesting the disappearance of viral **variants** with an alanine at this position under antiviral pressure exerted by **Nef** 128-137/136A-specific CTLs. In addition, 12 months after SIV challenge, six of eight clones from one macaque presented a glutamic acid at position 131 (**Nef** 128-137/131E+136T), which was not found in the infecting isolate. Furthermore, CTLs generated very early after SIV challenge were able to lyse cells sensitized with the **Nef** 128-137/136A epitope. In contrast, lysis was significantly less effective or even did not occur when either the selected **peptide Nef** 128-137/136T or the escape **variant peptide Nef** 128-137/131E+136T was used in a target cell sensitization assay. Dose analysis of **peptides** used to sensitize target cells as well as a major histocompatibility complex (MHC)-**peptide** stability assay suggested that the selected **peptide Nef** 128-137/136T has an altered capacity to bind to the MHC. These data suggest that CTL pressure leads to the selection of viral **variants** and to the emergence of escape mutants and supports the fact that immunization should elicit broad CTL responses.

L29 ANSWER 4 OF 4 MEDLINE
ACCESSION NUMBER: 95220421 MEDLINE
DOCUMENT NUMBER: 95220421 PubMed ID: 7705402
TITLE: HLA-dependent variations in human immunodeficiency virus **Nef** protein alter **peptide**/HLA binding.
AUTHOR: Couillin I; **Connan F**; Culmann-Penciolelli B; Gomard E; **Guillet J G**; Choppin J
CORPORATE SOURCE: Unite 152, Institut National de la Sante et de la Recherche Medicale, Institut Cochin de Genetique, Moleculaire, Paris, France.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Mar) 25 (3) 728-32. Journal code: 1273201. ISSN: 0014-2980.
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Journal; Article; (JOURNAL ARTICLE)
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AB In human immunodeficiency virus (HIV) infection, sequence variations within defined cytotoxic T lymphocyte (CTL) epitopes may lead to escape from CTL recognition. In a previous report, we have shown that the variable central region of HIV **Nef** protein (amino acids 73-144) that contains potential CTL epitopes, can escape the CTL response. We suggested that this non recognition occurs through a variety of mechanisms. In particular, we provided evidence that HIV **Nef** sequences recovered from HLA-A11-expressing individuals have alterations in the major anchor residues essential for binding of the two **Nef** epitopes (amino acids 73-82 and 84-92) to the HLA-A11 molecule. Here, we investigate in more detail whether variations in autologous **Nef** sequences affect HLA binding, leading to CTL escape. Potential epitopes were sought by testing **Nef peptides** containing the HLA-A11-specific motif or related motifs. We confirmed that only the two previously described epitopes identified in cytolysis tests have optimal reactivity with the HLA-A11 molecule. We then sequenced several viral **variants** from donors that do not express the HLA-A11 molecule and compared the variability of these epitopes with those obtained from HLA-A11-expressing individuals. One substitution (Leu85) found in the sequences isolated from both populations increase the reactivity of the HLA-A11-restricted epitope 84-92, and might explain the difference in immunogenicity observed between the two HLA-A11-restricted epitopes from HLA-A11+ individuals. In addition, selective variations were only detected in virus isolated from HLA-A11-expressing individuals. Furthermore, examination of the association of **variant peptides** with the HLA-A11 molecule demonstrated that a single substitution within the minimal epitope could not always completely abrogate HLA binding, suggesting that multiple alterations within a particular epitope may accumulate during disease progression, allowing the virus to escape CTL recognition.

=> dis his

(FILE 'HOME' ENTERED AT 12:18:33 ON 09 JUL 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:18:45 ON 09 JUL 2002
L1 20 S (NEF (1N) (84-92)) OR (GAG (1N) 77-85)
L2 5 DUP REM L1 (15 DUPLICATES REMOVED)
L3 207502 S ANALOGUE
L4 0 S L2 AND L3
L5 0 S L1 AND L3
L6 4675 S L3 AND HIV
L7 46831 S L3 (P) (PEPTIDE? OR PROTEIN?)
L8 184 S L7 (P) AIDS
L9 801 S L7 (P) (HIV OR NEF OR AIDS)
L10 847 S L7 (P) (HIV OR NEF OR AIDS OR GAG)
L11 110 S L7 (P) (NEF OR GAG)
L12 64 S L11 AND PD<19980507
L13 41 DUP REM L12 (23 DUPLICATES REMOVED)
L14 800 S L7 (P) (HIV OR AIDS)
L15 575 S L14 NOT NUCLEO?
L16 262 S L15 AND PD<19980507
L17 244 S L16 NOT L13
L18 155 DUP REM L17 (89 DUPLICATES REMOVED)

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L19          15 S L18 AND (NEF OR GAG)
L20        8085 S GUILLET J?/AU OR GUICHARD G?/AU OR OSTANKOVITCH M?/AU OR CONN
L21        1211 S L20 AND PEPTIDE?
L22          58 S L21 AND (GAG OR ENV)
L23          79 S L21 AND (GAG OR NEF)
L24          26 DUP REM L23 (53 DUPLICATES REMOVED)
L25           0 S L24 AND ANALOGUE?
L26           0 S L24 AND ANALOGU?
L27           0 S L24 AND ANALOG?
L28           4 S L24 AND VARIANT?
L29           4 S L24 AND VARIANT?
L30           0 S L24 AND DERIVATIV?

=> end
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
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